Appendix A

U.S. Pat. Appl. No. 09/518,501

Erion, *et al.*

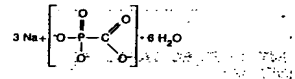
FOSCAVIR® Ⓡ

(foscarnet sodium) Injection
Ⓡ only

WARNING
RENAL IMPAIRMENT IS THE MAJOR TOXICITY OF FOSCAVIR. FREQUENT MONITORING OF SERUM CREATININE, WITH DOSE ADJUSTMENT FOR CHANGES IN RENAL FUNCTION, AND ADEQUATE HYDRATION WITH ADMINISTRATION OF FOSCAVIR, IS IMPERATIVE. (See ADMINISTRATION section; Hydration.)
SEIZURES, RELATED TO ALTERATIONS IN PLASMA MINERALS AND ELECTROLYTES, HAVE BEEN ASSOCIATED WITH FOSCAVIR TREATMENT. THEREFORE, PATIENTS MUST BE CAREFULLY MONITORED FOR SUCH CHANGES AND THEIR POTENTIAL SEQUELAE. MINERAL AND ELECTROLYTE SUPPLEMENTATION MAY BE REQUIRED.
FOSCAVIR IS INDICATED FOR USE ONLY IN IMMUNOCOMPROMISED PATIENTS WITH CMV RETINITIS AND MUCOCUTANEOUS ACYCLOVIR-RESISTANT HSV INFECTIONS. (See INDICATIONS section.)

DESCRIPTION

FOSCAVIR is the brand name for foscarnet sodium. The chemical name of foscarnet sodium is phosphonoformic acid, trisodium salt. Foscarnet sodium is a white, crystalline powder containing 6 equivalents of water of hydration with an empirical formula of $Na_3CO_2P^{\bullet}6\ H_2O$ and a molecular weight of 300.1. The structural formula is:



FOSCAVIR has the potential to chelate divalent metal ions, such as calcium and magnesium, to form stable coordination compounds. FOSCAVIR INJECTION is a sterile, isotonic aqueous solution for intravenous administration only. The solution is clear and colorless. Each milliliter of FOSCAVIR contains 24 mg of foscarnet sodium hexahydrate in Water for Injection, USP. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH of the solution to 7.4. FOSCAVIR INJECTION contains no preservatives.

HOW SUPPLIED

FOSCAVIR (foscarnet sodium) INJECTION, 24 mg/mL for intravenous infusion, is supplied in glass bottles as follows:
NDC 0186-1906-01 500 mL bottles, cases of 12
NDC 0186-1905-01 250 mL bottles, cases of 12
FOSCAVIR INJECTION should be stored at controlled room temperature, 15–30°C (59–86°F), and should be protected from excessive heat (above 40°C) and from freezing. FOSCAVIR INJECTION should be used only if the bottle and seal are intact, a vacuum is present, and the solution is clear and colorless.

Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: Abbott Laboratories, North Chicago, IL 60064
700571-12
Rev. 7/02

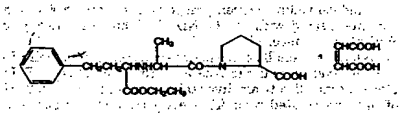
LEXXEL® Ⓡ

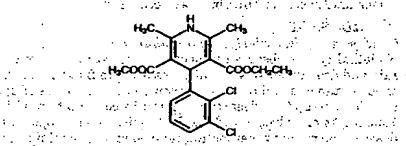
(enalapril maleate-felodipine ER)
TABLETS

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, LEXXEL should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

LEXXEL (enalapril maleate-felodipine ER) is a combination product, consisting of an outer layer of enalapril maleate surrounding a core tablet of an extended-release felodipine formulation.
Enalapril maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5 \bullet C_4H_4O_4$, and its structural formula is:
[See chemical structure at top of next column]
Enalapril maleate is a white to off-white, crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.
Felodipine, a calcium channel blocker, is a dihydropyridine derivative that is chemically described as ± ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. Its empirical formula is $C_{18}H_{19}Cl_2NO_4$ and its structural formula is:





Felodipine is a slightly yellowish, crystalline powder with a molecular weight of 384.26. It is insoluble in water and is freely soluble in dichloromethane and ethanol. Felodipine is a racemic mixture; however, S-felodipine is the more biologically active enantiomer.
LEXXEL is available for oral use in two tablet combinations of enalapril maleate with felodipine as an extended-release formulation: LEXXEL 5-2.5, containing 5 mg of enalapril maleate and 2.5 mg of felodipine ER and LEXXEL 5-5, containing 5 mg of enalapril maleate and 5 mg of felodipine ER. Inactive ingredients include propyl gallate, polyoxyl 40 hydrogenated castor oil, cellulose compounds, lactose, aluminum silicate, sodium stearyl fumarate, carnauba wax, and iron oxides. The tablets are imprinted with an ink of synthetic red iron oxide (LEXXEL 5-2.5) or synthetic black iron oxide (LEXXEL 5-5) which contains pharmaceutical glaze in SD-45, n-butyl alcohol, propylene glycol, isopropyl alcohol, ammonium hydroxide, and simethicone (LEXXEL 5-2.5) and methyl alcohol (LEXXEL 5-5).

HOW SUPPLIED

No. 3771—Tablets LEXXEL 5-2.5 are white, round/biconvex-shaped, film-coated tablets, coded LEXXEL 2, 5-2.5 on one side and no markings on the other. Each tablet contains 5 mg of enalapril maleate and 2.5 mg of felodipine as an extended-release formulation. They are supplied as follows:
NDC 0186-0002-31 unit of use bottles of 30 (with desiccants)
No. 3661—Tablets LEXXEL 5-5 are white, round/biconvex-shaped, film-coated tablets, coded LEXXEL 1, 5-5 on one side and no markings on the other. Each tablet contains 5 mg of enalapril maleate and 5 mg of felodipine as an extended-release formulation. They are supplied as follows:
NDC 0186-0001-31 unit of use bottles of 30 (with desiccants)
NDC 0186-0001-68 bottles of 100 (with desiccants)

Storage

Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. Keep container tightly closed. Protect from moisture and light. Dispense in a tight container, if product package is subdivided.
Rev. 11/03
LEXXEL is a trademark of the AstraZeneca group

Manufactured for: AstraZeneca LP
Wilmington, DE 19850
By: Merck & Co., Inc., Whitehouse Station, NJ 08889, USA
9176508
620008-08
Rev. 11/03

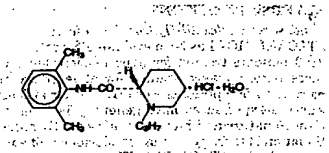
Shown in Product Identification Guide, page 305

NAROPIN® Ⓡ

[nă'rō-pĭn]
(ropivacaine HCl) Injection
Ⓡ only

DESCRIPTION

Naropin® Injection contains ropivacaine HCl which is a member of the amino amide class of local anesthetics. Naropin Injection is a sterile, isotonic solution that contains the enantiomerically pure drug substance, sodium chloride for isotonicity and Water for Injection. Sodium hydroxide and/or hydrochloric acid may be used for pH adjustment. It is administered parenterally.
Ropivacaine HCl is chemically described as S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate. The drug substance is a white crystalline powder, with a molecular formula of $C_{17}H_{26}N_2O \bullet HCl \bullet H_2O$, molecular weight of 328.89 and the following structural formula:
[See chemical structure at top of next column]
At 25°C ropivacaine HCl has a solubility of 53.8 mg/mL in water, a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 14:1 and a pKa of 8.07 in 0.1 M KCl solution. The pKa of ropivacaine is approximately the same as bupivacaine (8.1) and is similar to that of mepivacaine (7.7). However, ropivacaine has an intermediate degree of lipid solubility compared to bupivacaine and mepivacaine.
Naropin Injection is preservative-free and is available in single dose containers in 2.0 (0.2%), 5.0 (0.5%), 7.5 (0.75%) and 10.0 mg/mL(1.0%) concentrations. The specific gravity of Naropin solutions range from 1.002 to 1.005 at 25°C.



CLINICAL PHARMACOLOGY

Mechanism of Action

Ropivacaine is a member of the amino amide class of local anesthetics and is supplied as the pure S-(-)-enantiomer. Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

PHARMACOKINETICS

Absorption

The systemic concentration of ropivacaine is dependent on the total dose and concentration of drug administered, the route of administration, the patient's hemodynamic/circulatory condition, and the vascularity of the administration site.
From the epidural space, ropivacaine shows complete and biphasic absorption. The half-lives of the 2 phases (mean ± SD) are 14 ± 7 minutes and 4.2 ± 0.9 h, respectively. The slow absorption is the rate limiting factor in the elimination of ropivacaine which explains why the terminal half-life is longer after epidural than after intravenous administration.
Ropivacaine shows dose-proportionality up to the highest intravenous dose studied, 80 mg, corresponding to a mean ± SD peak plasma concentration of 1.9 ± 0.3 µg/mL.
[See table 1 at top of next page]
In some patients after a 300 mg dose for brachial plexus block, free plasma concentrations of ropivacaine may approach the threshold for CNS toxicity. (See PRECAUTIONS.) At a dose of greater than 300 mg, for local infiltration, the terminal half-life may be longer (≥30 hours).

Distribution

After intravascular infusion, ropivacaine has a steady state volume of distribution of 41 ± 7 liters. Ropivacaine is 94% protein bound, mainly to α-acid glycoprotein. An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a postoperative increase of α_1-acid glycoprotein. Variations in unbound, ie, pharmacologically active, concentrations have been less than in total plasma concentration. Ropivacaine readily crosses the placenta and equilibrium in regard to unbound concentration will be rapidly reached. (See PRECAUTIONS, Labor and Delivery.)

Metabolism

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P4501A to 3-hydroxy ropivacaine. After a single IV dose approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. Low concentrations of 3-hydroxy ropivacaine have been found in the plasma. Urinary excretion of the 4-hydroxy ropivacaine, and both the 3-hydroxy N-de-alkylated (3-OH-PPX) and 4-hydroxy N-de-alkylated (4-OH-PPX) metabolites account for less than 3% of the dose. An additional metabolite, 2-hydroxy-methyl-ropivacaine, has been identified but not quantified in the urine. The N-de-alkylated metabolite of ropivacaine (PPX) and 3-OH-ropivacaine are the major metabolites excreted in the urine during epidural infusion. Total PPX concentration in the plasma was about half as that of total ropivacaine; however, mean unbound concentrations of PPX was about 7 to 9 times higher than that of unbound ropivacaine following continuous epidural infusion up to 72 hours. Unbound PPX, 3-hydroxy and 4-hydroxy ropivacaine, have a pharmacological activity in animal models less than that of ropivacaine. There is no evidence of *in vivo* racemization in urine of ropivacaine.

Elimination

The kidney is the main excretory organ for most local anesthetic metabolites. In total, 86% of the ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug. Ropivacaine has a mean ± SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min, and a renal clearance of 1 mL/min. The mean ± SD terminal half-life is 1.8 ± 0.7 h after intravascular administration and 4.2 ± 1.0 h after epidural administration (see Absorption).

Pharmacodynamics

Studies in humans have demonstrated that, unlike most other local anesthetics, the presence of epinephrine has no major effect on either the time of onset or the duration of action of ropivacaine. Likewise, addition of epinephrine to ropivacaine has no effect on limiting systemic absorption of ropivacaine.
Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance have been reported. Toxic blood concentrations depress cardiac conduction and

Campath—Cont.

Gastrointestinal System Disorders: duodenal ulcer, esophagitis, gingivitis, gastroenteritis, GI hemorrhage, hematemesis, hemorrhoids, intestinal obstruction, intestinal perforation, melena, paralytic ileus, peptic ulcer, pseudomembranous colitis, colitis, pancreatitis, peritonitis, hyperbilirubinemia, hepatic failure, hepatocellular damage, hypoalbuminemia, biliary pain

Hearing and Vestibular Disorders: decreased hearing

Metabolic and Nutritional Disorders: acidosis, aggravated diabetes mellitus, dehydration, fluid overload, hyperglycemia, hyperkalemia, hypokalemia, hypoglycemia, hyponatremia, increased alkaline phosphatase, respiratory alkalosis

Musculoskeletal System Disorders: arthritis or worsening arthritis, arthropathy, bone fracture, myositis, muscle atrophy, muscle weakness, osteomyelitis, polymyositis

Neoplasms: malignant lymphoma, malignant testicular neoplasm, prostatic cancer, plasma cell dyscrasia, secondary leukemia squamous cell carcinoma, transformation to aggressive lymphoma, transformation to prolymphocytic leukemia

Platelet, Bleeding, and Clotting Disorders: coagulation disorder, disseminated intravascular coagulation, hematoma, pulmonary embolism, thrombocythemia

Psychiatric Disorders: confusion, hallucinations, nervousness, abnormal thinking, apathy

White Cell and RES Disorders: agranulocytosis, aplasia, decreased haptoglobin, lymphadenopathy, marrow depression

Red Blood Cell Disorders: hemolysis, hemolytic anemia, splenic infarction, splenomegaly

Reproductive System Disorders: cervical dysplasia

Resistance Mechanism Disorders: abscess, bacterial infection, *Herpes zoster* infection, *Pneumocystis carinii* infection, otitis media, Tuberculosis infection, viral infection

Respiratory System Disorders: asthma, bronchitis, chronic obstructive pulmonary disease, hemoptysis, hypoxia, pleural effusion pleurisy, pneumothorax, pulmonary edema, pulmonary fibrosis, pulmonary infiltration, respiratory depression, respiratory insufficiency, sinusitis, stridor, throat tightness

Skin and Appendages Disorders: angioedema, bullous eruption, cellulitis, purpuric rash

Special Senses Disorders: taste loss

Urinary System Disorders: abnormal renal function, acute renal failure, anuria, facial edema, hematuria, toxic nephropathy ureteric obstruction, urinary retention, urinary tract infection

Vascular (Extracardiac) Disorders: cerebral hemorrhage, cerebrovascular disorder, deep vein thrombosis, increased capillary fragility, intracranial hemorrhage, phlebitis, subarachnoid hemorrhage, thrombophlebitis

Vision Disorders: endophthalmitis

OVERDOSAGE

Initial doses of Campath of greater than 3 mg are not well-tolerated. One patient who received 80 mg as an initial dose by IV infusion experienced acute bronchospasm, cough, and shortness of breath, followed by anuria and death. A review of the case suggested that tumor lysis syndrome may have played a role.

Single doses of Campath greater than 30 mg or a cumulative weekly dose greater than 90 mg should not be administered as higher doses have been associated with a higher incidence of pancytopenia. (See BOXED WARNING and DOSAGE AND ADMINISTRATION.)

There is no known specific antidote for Campath overdosage. Treatment consists of drug discontinuation and supportive therapy.

DOSAGE AND ADMINISTRATION

Campath should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Dosing Schedule and Administration: Campath therapy should be initiated at a dose of 3 mg administered as a 2 hour IV infusion daily. (See ADVERSE EVENTS.) When the Campath 3 mg daily dose is tolerated (e.g., infusion-related toxicities are ≤ Grade 2), the daily dose should be escalated to 10 mg and continued until tolerated. When the 10 mg dose is tolerated, the maintenance dose of Campath 30 mg may be initiated. The maintenance dose of Campath is 30 mg/day administered three times per week on alternate days (i.e., Monday, Wednesday, and Friday) for up to 12 weeks. In most patients, escalation to 30 mg can be accomplished in 3–7 days. **Dose escalation to the recommended maintenance dose of 30 mg administered three times per week is required. Single doses of Campath greater than 30 mg or cumulative weekly doses of greater than 90 mg should not be administered since higher doses are associated with an increased incidence of pancytopenia.** (See BOXED WARNING.) Campath should be administered intravenously only. The infusion should be administered over a 2 hour period. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.**

Recommended Concomitant Medications: Premedication should be given prior to the first dose, at dose escalations, and as clinically indicated. The premedicaton used in clinical studies was diphenhydramine 50 mg and acetaminophen 650 mg administered 30 minutes prior to Campath infusion. In cases where severe infusion-related events occur, treatment with hydrocortisone 200 mg was used in decreasing the infusion-related events.

Patients should receive anti-infective prophylaxis to minimize the risks of serious opportunistic infections. (See BOXED WARNING.) The anti-infective regimen used on Study 1 consisted of trimethoprim/sulfamethoxazole DS twice daily (BID) three times per week and famciclovir or equivalent 250 mg twice a day (BID) upon initiation of Campath therapy. Prophylaxis should be continued for 2 months after completion of Campath therapy or until the $CD4^+$ count is ≥ 200 cells/μL, whichever occurs later.

Dose Modification and Reinitiation of Therapy: Campath therapy should be discontinued during serious infection, serious hematologic toxicity, or other serious toxicity until the event resolves. (See WARNINGS.) Campath therapy should be permanently discontinued if evidence of autoimmune anemia or thrombocytopenia appears. Table 3 includes recommendations for dose modification for severe neutropenia or thrombocytopenia.

(See table 3 below)

Preparation for Administration:

Parenteral drug products should be inspected for visible particulate matter and discoloration prior to administration. If particulate matter is present or the solution is discolored, the vial should not be used. **DO NOT SHAKE AMPOULE PRIOR TO USE.** As with all parenteral drug products, aseptic technique should be used during the preparation and administration of Campath. Withdraw the necessary amount of Campath from the ampoule into a syringe. Filter with a sterile, low-protein binding, non-fiber releasing 5 μm filter prior to dilution.

Inject into 100 mL sterile 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. **Gently invert the bag to mix the solution.** Discard syringe and any unused drug product.

Campath contains no antimicrobial preservative. Campath should be used within 8 hours after dilution. Campath solutions may be stored at room temperature (15–30°C) or refrigerated. Campath solutions should be protected from light.

Incompatibilities:

No incompatibilities between Campath and polyvinylchloride (PVC) bags, PVC or polyethylene-lined PVC administration sets, or low-protein binding filters have been observed. No data are available concerning the incompatibility of Campath with other drug substances. Other drug substances should not be added or simultaneously infused through the same intravenous line.

HOW SUPPLIED

Campath (Alemtuzumab) is supplied in single-use clear glass ampoules containing 30 mg of Alemtuzumab in 3 mL of solution. Each box contains three Campath ampoules (NDC 50419-355-10).

Campath should be stored at 2–8°C (36–46°F). Do not freeze. DISCARD IF AMPOULE HAS BEEN FROZEN. Protect from direct sunlight.

Rx only.

Table 3: Dose Modification and Reinitiation of Therapy for Hematologic Toxicity

Hematologic Toxicity	Dose Modification and Reinitiation of Therapy
For first occurrence of ANC <250/μL and/or platelet count ≤25,000/μL	Withhold Campath therapy. When ANC ≥500/μL and platelet count ≥50,000/μL, resume Campath therapy at same dose. If delay between dosing is ≥7 days, initiate therapy at Campath 3 mg and escalate to 10 mg and then to 30 mg as tolerated.
For second occurrence of ANC <250/μL and/or platelet count ≤25,000/μL	Withhold Campath therapy. When ANC ≥500/μL and platelet count ≥50,000/μL, resume Campath therapy at 10 mg. If delay between dosing is ≥7 days, initiate therapy at Campath 3 mg and escalate to 10 mg only.
For third occurrence of ANC <250/μL and/or platelet count ≤25,000/μL	Discontinue Campath therapy permanently.
For a decrease of ANC and/or platelet count to ≤50% of the baseline value in patients initiating therapy with a baseline ANC ≤500/μL and/or a baseline platelet count ≤25,000/μL	Withhold Campath therapy. When ANC and/or platelet count return to baseline value(s), resume Campath therapy. If the delay between dosing ≥7 days, initiate therapy at Campath 3 mg and escalate to 10 mg and then to 30 mg as tolerated.

U.S. Patents: 5,545,403; 5,545,405; 5,654,403; 5,846,534
Other patents pending
Manufactured by: ILEX Pharmaceuticals, LP., San Antonio, TX 78229
Distributed by:
BERLEX® Laboratories, Richmond, CA 94804
Issued: January 2002

42946/USP

FLUDARA®

(flū 'dar-ă) B

(fludarabine phosphate)

FOR INJECTION

FOR INTRAVENOUS USE ONLY

Rx Only

WARNING: FLUDARA FOR INJECTION should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. FLUDARA FOR INJECTION can severely suppress bone marrow function. When used at high doses in dose-ranging studies in patients with acute leukemia, FLUDARA FOR INJECTION was associated with severe neurologic effects, including blindness, coma, and death. This severe central nervous system toxicity occurred in 36% of patients treated with doses approximately four times greater (96 mg/m²/day for 5-7 days) than the recommended dose. Similar severe central nervous system toxicity has been rarely (≤0.2%) reported in patients treated at doses in the range of the dose recommended for chronic lymphocytic leukemia.

Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with FLUDARA FOR INJECTION. Patients undergoing treatment with FLUDARA FOR INJECTION should be evaluated and closely monitored for hemolysis.

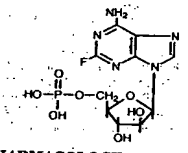
In a clinical investigation using FLUDARA FOR INJECTION in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of FLUDARA FOR INJECTION in combination with pentostatin is not recommended.

DESCRIPTION

FLUDARA FOR INJECTION contains fludarabine phosphate, a fluorinated nucleotide analog of the antiviral agent vidarabine, 9-β-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase. Each vial of sterile lyophilized solid cake contains 50 mg of the active ingredient fludarabine phosphate, 50 mg of mannitol, and sodium hydroxide to adjust pH to 7.7. The pH range for the final product is 7.2-8.2. Reconstitution with 2 mL of Sterile Water for Injection USP results in a solution containing 25 mg/mL of fludarabine phosphate intended for intravenous administration.

The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-O-phosphono-β-D-arabinofuranosyl) (2-fluoro-ara-AMP).

The molecular formula of fludarabine phosphate is $C_{10}H_{13}FN_5O_7P$ (MW 365.2) and the structure is:



CLINICAL PHARMACOLOGY

Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP. This metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. The mechanism of action of this antimetabolite is not completely characterized and may be multi-faceted.

Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted to the active metabolite, 2-fluoro-ara-A, within minutes after intravenous infusion. Consequently, clinical pharmacology studies have focused on 2-fluoro-ara-A pharmacokinetics. After the five daily doses of 25 mg 2-fluoro-ara-AMP/m² to cancer patients infused over 30 minutes, 2-fluoro-ara-A concentrations show a moderate accumulation. During a 5-day treatment schedule, 2-fluoro-ara-A plasma trough levels increased by a factor of about 2. The terminal half-life of 2-fluoro-ara-A was estimated as approximately 20 hours. *In vitro*, plasma protein binding of fludarabine ranged between 19% and 29%. A correlation was noted between the degree of absolute granulocyte count nadir and increased area under the concentration × time curve (AUC).

Special Populations

Pediatric Patients

Limited pharmacokinetic data for FLUDARA FOR INJECTION are available from a published study of chil-

Metadate ER—Cont.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

CONTRAINDICATIONS

Marked anxiety, tension and agitation are contraindications to METADATE ER, since the drug may aggravate these symptoms. METADATE ER is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.

METADATE ER is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

METADATE ER should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e. weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored.

METADATE ER should not be used for severe depression of either exogenous or endogenous origin. Clinical experience suggests that in psychotic children, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder.

METADATE ER should not be used for the prevention or treatment of normal fatigue states.

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. Safe concomitant use of anticonvulsants and METADATE ER has not been established. In the presence of seizures, the drug should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking METADATE ER, especially those with hypertension.

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Drug Interactions: METADATE ER may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, phenytoin, primidone), phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with METADATE ER.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.

Usage in Pregnancy: Adequate animal reproduction studies to establish safe use of methylphenidate during pregnancy have not been conducted. Therefore, until more information is available, METADATE ER should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

Drug Dependence: METADATE® ER Tablets (methylphenidate hydrochloride extended-release tablets, USP) should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative.

Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

PRECAUTIONS

Patients with an element of agitation may react adversely; discontinue therapy if necessary.

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Drug treatment is not indicated in all cases of this behavioral syndrome and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe METADATE® ER Tablets (methylphenidate hydrochloride extended-release tablets, USP) should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics.

When these symptoms are associated with acute stress reactions, treatment with methylphenidate is usually not indicated.

Long-term effects of methylphenidate in children have not been well established.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 2.5 times the maximum recommended human dose on a mg/kg and mg/m^2 basis respectively.

Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 4 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. The genotoxic potential of methylphenidate has not been evaluated in an *in vivo* assay.

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

OVERDOSAGE

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Consult with a Certified Poison Control Center regarding treatment for up-to-date guidance and advice.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage. In the presence of severe intoxication, use a carefully titrated dosage of a *short-acting* barbiturate *before* performing gastric lavage.

Other measures to detoxify the gut include administration of activated charcoal and a cathartic.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for methylphenidate overdosage has not been established.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the needs and responses of the patient.

Adults: *Methylphenidate Hydrochloride, USP Immediate-Release Tablets:* Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10 to 15 mg daily will be adequate. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 p.m.

Extended-Release Tablets: METADATE ER Tablets have a duration of action of approximately 8 hours. Therefore, the extended-release tablets may be used in place of the immediate-release tablets when the 8-hour dosage of METADATE ER Tablets corresponds to the titrated 8-hour dosage of the immediate-release tablets. METADATE ER Tablets must be swallowed whole and never crushed or chewed.

Children (6 years and over): Methylphenidate hydrochloride tablets should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

Methylphenidate Hydrochloride, USP Immediate-Release Tablets: Start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly.

Extended-Release Tablets: METADATE ER Tablets have a duration of action of approximately 8 hours. Therefore, the extended-release tablets may be used in place of the immediate-release tablets when the 8-hour dosage of METADATE ER Tablets corresponds to the titrated 8-hour dosage of the immediate-release tablets. METADATE ER Tablets must be swallowed whole and never crushed or chewed.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

METADATE ER should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

HOW SUPPLIED

METADATE ER Tablets (methylphenidate hydrochloride extended-release tablets, USP) are available as follows:

10 mg: Oval, white, uncoated, unscored, debossed "561 MD".
NDC 53014-593-07 Bottle of 100's

20 mg: Round, white, uncoated, unscored, debossed "562 MD".
NDC 53014-594-07 Bottle of 100's

NOTE: METADATE ER Tablets are color-additive free.

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP with a child-resistant closure. Store at controlled room temperature 15°–30°C (59°–86°F). [See USP.] Protect from moisture.

Celltech Pharmaceuticals, Inc.
Rochester, NY 14623 USA
®Celltech Pharma Limited.

Rev. 6/02
R533A

PEDIAPRED®

℞

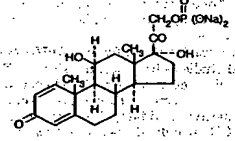
(prednisolone sodium phosphate, USP)
Oral Solution
℞ **Only**

R529
Rev. 7/01

DESCRIPTION

PEDIAPRED (prednisolone sodium phosphate, USP) Oral Solution is a dye free, colorless to light straw colored, raspberry flavored solution. Each 5 mL (teaspoonful) of PEDIAPRED contains 6.7 mg prednisolone sodium phosphate (5 mg prednisolone base) in a palatable, aqueous vehicle.

PEDIAPRED also contains dibasic sodium phosphate, edetate disodium, methylparaben, purified water, sodium biphosphate, sorbitol, natural and artificial raspberry flavor. Prednisolone sodium phosphate occurs as white or slightly yellow, friable granules or powder. It is freely soluble in water; soluble in methanol; slightly soluble in alcohol and in chloroform; and very slightly soluble in acetone and in dioxane. The chemical name of prednisolone sodium phosphate is pregna-1,4-diene-3,20-dione,11,17-dihydroxy-21-(phosphonooxy)-, disodium salt, (11β)-. The empirical formula is $C_{21}H_{27}Na_2O_8P$; the molecular weight is 484.39. Its chemical structure is:



Pharmacological Category: Glucocorticoid

...WARNING: ...May be habit-forming ... 650 mg

...SUPPLIED
...each tablet of which contains hydrocodone ...mg (WARNING: May be habit-forming) and ...650 mg, are white, capsule-shaped, scored ...nosed "U" on one side and "201" on the other ...is supplied in containers of 100 tablets, NDC ...01; containers of 500 tablets, NDC #0785-1122-...unit-dose cartons of 100 tablets (4 cards of 25 ...each), NDC #0785-1122-63.
...in Product Identification Guide, page 312

...ORCET® 10/650 Ⓡ
...DROCODONE BITARTRATE ...D ACETAMINOPHEN TABLETS USP
...g/650 mg

DESCRIPTION

...Lorcet® 10/650 tablet contains:
...Hydrocodone ... 10 mg
...Bitartrate
WARNING: May be habit-forming
...Acetaminophen ... 650 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid and FD&C Blue #1 Lake.

This product complies with Dissolution Test 1.

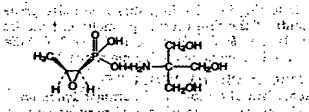
HOW SUPPLIED

Lorcet® 10/650, Hydrocodone Bitartrate and Acetaminophen Tablets, each tablet of which contains hydrocodone bitartrate 10 mg (WARNING: May be habit-forming) and acetaminophen 650 mg, are light-blue, capsule-shaped, scored tablets, debossed "UAD" on one side and "63 50" on the other side, and are supplied in containers of 100 tablets, NDC 0785-6350-01 and in containers of 500 tablets, NDC 0785-6350-50, and in containers of unit dose (4 × 25's), NDC 0785-6350-63.
Shown in Product Identification Guide, page 312

MONUROL® Ⓡ
[mon ur ol]
(fosfomycin tromethamine)
SACHET
...g only

DESCRIPTION

MONUROL (fosfomycin tromethamine) sachet contains fosfomycin tromethamine, a synthetic, broad-spectrum, bactericidal antibiotic for oral administration. It is available as a single-dose sachet which contains white granules consisting of 5.631 grams of fosfomycin tromethamine (equivalent to 3 grams of fosfomycin), and the following inactive ingredients: mandarin flavor, orange flavor, saccharin, and sucrose. The contents of the sachet must be dissolved in water. Fosfomycin tromethamine, a phosphonic acid derivative, is available as (1*R*,2*S*)-(1,2-epoxypropyl)phosphonic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). It is a white granular compound with a molecular weight of 259.2. Its empirical formula is $C_3H_7O_4P{\cdot}C_4H_{11}NO_3$, and its chemical structure is as follows:



CLINICAL PHARMACOLOGY

Absorption: Fosfomycin tromethamine is rapidly absorbed following oral administration and converted to the free acid, fosfomycin. Absolute oral bioavailability under fasting conditions is 37%. After a single 3-gm dose of MONUROL, the mean (± 1 SD) maximum serum concentration (C_{max}) achieved was 26.1 (± 9.1) µg/mL within 2 hours. The oral bioavailability of fosfomycin is reduced to 30% under fed conditions. Following a single 3-gm oral dose of MONUROL with a high-fat meal, the mean C_{max} achieved was 17.6 (± 4.4) µg/mL within 4 hours.
Cimetidine does not affect the pharmacokinetics of fosfomycin when coadministered with MONUROL. Metoclopramide lowers the serum concentrations and urinary excretion of fosfomycin when coadministered with MONUROL. (See **PRECAUTIONS, Drug Interactions.**)
Distribution: The mean apparent steady-state volume of distribution (V_{SS}) is 136.1 (±44.1) L following oral administration of MONUROL. Fosfomycin is not bound to plasma proteins.
Fosfomycin is distributed to the kidneys, bladder wall, prostate, and seminal vesicles. Following a 50 mg/Kg dose of fosfomycin to patients undergoing urological surgery for bladder carcinoma, the mean concentration of fosfomycin in the bladder, taken at a distance from the neoplastic site, was 18.0 µg per gram of tissue at 3 hours after dosing. Fosfomycin has been shown to cross the placental barrier in animals and man.
Excretion: Fosfomycin is excreted unchanged in both urine and feces. Following oral administration of MONUROL, the mean total body clearance ($CL_{T/F}$) and mean renal clearance (CL_R) of fosfomycin were 16.9 (±3.5) L/hr and 6.3 (± 1.7) L/hr, respectively. Approximately 38% of a 3-gm dose of MONUROL is recovered from urine, and 18% is recovered from feces. Following intravenous administration, the mean $CL_{T/B}$ and mean CL_R of fosfomycin were 6.1 (± 1.0) L/hr and 5.5 (± 1.2) L/hr, respectively.
A mean urine fosfomycin concentration of 706 (± 466) µg/mL was attained within 2–4 hours after a single oral 3-gm dose of MONUROL under fasting conditions. The mean urinary concentration of fosfomycin was 10 µg/mL in samples collected 72–84 hours following a single oral dose of MONUROL.
Following a 3-gm dose of MONUROL administered with a high fat meal, a mean urine fosfomycin concentration of 537 (± 252) µg/mL was attained within 6–8 hours. Although the rate of urinary excretion of fosfomycin was reduced under fed conditions, the cumulative amount of fosfomycin excreted in the urine was the same, 1118 (± 201) mg (fed) vs. 1140 mg (±238) (fasting). Further, urinary concentrations equal to or greater than 100 µg/mL were maintained for the same duration, 26 hours, indicated that MONUROL can be taken without regard to food.
Following oral administration of MONUROL, the mean half-life for elimination ($t_{1/2}$) is 5.7 (± 2.8) hours.
Special Populations:
Geriatric: Based on limited data regarding 24-hour urinary drug concentrations, no differences in urinary excretion of fosfomycin have been observed in elderly subjects. No dosage adjustment is necessary in the elderly.
Gender: There are no gender differences in the pharmacokinetics of fosfomycin.
Renal Insufficiency: In 5 anuric patients undergoing hemodialysis, the $t_{1/2}$ of fosfomycin during hemodialysis was 40 hours. In patients with varying degrees of renal impairment (creatinine clearances varying from 54 mL/min to 7 mL/min), the $t_{1/2}$ of fosfomycin increased from 11 hours to 50 hours. The percent of fosfomycin recovered in urine decreased from 32% to 11% indicating that renal impairment significantly decreases the excretion of fosfomycin.
Microbiology
Fosfomycin (the active component of fosfomycin tromethamine) has *in vitro* activity against a broad range of gram-positive and gram-negative aerobic microorganisms which are associated with uncomplicated urinary tract infections. Fosfomycin is bactericidal in urine at therapeutic doses. The bactericidal action of fosfomycin is due to its inactivation of the enzyme enolpyruvyl transferase, thereby irreversibly blocking the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate, one of the first steps in bacterial cell wall synthesis. It also reduces adherence of bacteria to uroepithelial cells.
There is generally no cross-resistance between fosfomycin and other classes of antibacterial agents such as beta-lactams and aminoglycosides.
Fosfomycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:
Aerobic gram-positive microorganisms
Enterococcus faecalis
Aerobic gram-negative microorganisms
Escherichia coli
The following *in vitro* data are available, but their clinical significance is unknown.
Fosfomycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 64 µg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of fosfomycin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:
Aerobic gram-positive microorganisms
Enterococcus faecium
Aerobic gram-negative microorganisms
Citrobacter diversus
Citrobacter freundii
Enterobacter aerogenes
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Proteus vulgaris
Serratia marcescens
SUSCEPTIBILITY TESTING
Dilution Techniques:
Quantitative methods are used to determine minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized agar dilution method[1] or equivalent with standardized inoculum concentrations and standardized concentrations of fosfomycin tromethamine (in terms of fosfomycin base content) powder supplemented with 25 µg/mL of glucose-6-phosphate. **BROTH DILUTION METHODS SHOULD NOT BE USED TO TEST SUSCEPTIBILITY TO FOSFOMYCIN.** The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 64	Susceptible (S)
128	Intermediate (I)
≥ 256	Resistant (R)

A report of "susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in the urine. A report of "intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that usually achievable concentrations of the antimicrobial compound in the urine are unlikely to be inhibitory and that other therapy should be selected.
Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard fosfomycin tromethamine powder should provide the following MIC values for agar dilution testing in media containing 25 µg/mL of glucose-6-phosphate. (Broth dilution testing should not be performed):

Microorganism	MIC (µg/mL)
Enterococcus faecalis ATCC 29212	32–128
Escherichia coli ATCC 25922	0.5–2
Pseudomonas aeruginosa ATCC 27853	2–8
Staphylococcus aureus ATCC 29213	0.5–4

Diffusion Techniques:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial agents. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 200-µg fosfomycin and 50-µg of glucose-6-phosphate to test the susceptibility of microorganisms to fosfomycin.
Reports from the laboratory providing results of the standard single-disk susceptibility test with disks containing 200 µg of fosfomycin and 50 µg of glucose-6-phosphate should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥16	Susceptible (S)
13–15	Intermediate (I)
≤12	Resistant (R)

Interpretation should be stated as above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for fosfomycin.
As with standardized dilution techniques, diffusion methods require use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 200-µg fosfomycin disk with the 50-µg of glucose-6-phosphate should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter (mm)
Escherichia coli ATCC 25922	22–30
Staphylococcus aureus ATCC 25923	25–33

INDICATIONS AND USAGE
MONUROL is indicated only for the treatment of uncomplicated urinary tract infections (acute cystitis) in women due to susceptible strains of *Escherichia coli* and *Enterococcus faecalis*. MONUROL is not indicated for the treatment of pyelonephritis or perinephric abscess.
If persistence or reappearance of bacteriuria occurs after treatment with MONUROL, other therapeutic agents should be selected. (See **PRECAUTIONS** and **CLINICAL STUDIES** section.)
CONTRAINDICATIONS
MONUROL is contraindicated in patients with known hypersensitivity to the drug.
PRECAUTIONS
General
Do not use more than one single dose of MONUROL to treat a single episode of acute cystitis. Repeated daily doses of MONUROL did not improve the clinical success or microbiological eradication rates compared to single dose therapy, but did increase the incidence of adverse events.
Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy.
Information for Patients
Patients should be informed:
- That MONUROL (fosfomycin tromethamine) can be taken with or without food.
- That their symptoms should improve in two to three days after taking MONUROL; if not improved, the patient should contact her health care provider.

Drug Interactions
Metoclopramide: When coadministered with MONUROL, metoclopramide, a drug which increases gastrointestinal motility, lowers the serum concentration and urinary excretion of fosfomycin. Other drugs that increase gastrointestinal motility may produce similar effects.
Cimetidine: Cimetidine does not affect the pharmacokinetics of fosfomycin when coadministered with MONUROL.

Continued on next page

other antiretroviral agents for periods of 10 days to 200 weeks in Phase I-III clinical trials.

Assessment of adverse reactions is based on data from studies 301A and 303 in which 571 treatment naive (301A) and 440 treatment experienced (303) patients received EMTRIVA 200 mg (n=580) or comparator drug (n=431) for 48 weeks.

The most common adverse events that occurred in patients receiving EMTRIVA with other antiretroviral agents in clinical trials were headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All adverse events were reported with similar frequency in EMTRIVA and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the EMTRIVA treated group.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

A summary of EMTRIVA treatment emergent clinical adverse events in studies 301A and 303 is provided in Table 6 below.

[See table 6 on previous page]

Laboratory Abnormalities:

Laboratory abnormalities in these studies occurred with similar frequency in the EMTRIVA and comparator groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 7 below.

[See table 7 on previous page]

OVERDOSAGE

There is no known antidote for EMTRIVA. Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported.

The effects of higher doses are not known. If overdose occurs the patient should be monitored for signs of toxicity, and standard supportive treatment applied as necessary.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

For adults 18 years of age and older, the dose of EMTRIVA is 200 mg once daily taken orally with or without food.

Dose Adjustment in Patients with Renal Impairment:

Significantly increased drug exposures were seen when EMTRIVA was administered to patients with renal impairment, (see CLINICAL PHARMACOLOGY: Special Populations). Therefore, the dosing interval of EMTRIVA should be adjusted in patients with baseline creatinine clearance < 50 mL/min using the following guidelines (see Table 8). The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

[See table 8 on previous page]

HOW SUPPLIED

EMTRIVA is available as capsules. EMTRIVA capsules, 200 mg, are size 1 hard gelatin capsules with a blue cap and white body, printed with "200 mg" in black on the cap and "GILEAD" and the corporate logo in black on the body. They are packaged in bottles of 30 capsules (NDC 61958-0501-1) with induction sealed child-resistant closures.

Store at 25 °C (77 °F); excursions permitted to 15 °C–30 °C (59 °F–86 °F) [see USP Controlled Room Temperature].

EMTRIVA is manufactured for Gilead Sciences, Inc., Foster City, CA 94404.

July 2003

EMTRIVA™ is a trademark of Gilead Sciences, Inc.

R24-1466

Shown in Product Identification Guide, page 313

HEPSERA™ R
[hep' sĕr-ă]
adefovir dipivoxil Tablets
30 Only

WARNINGS

1. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED ANTI-HEPATITIS B THERAPY, INCLUDING THERAPY WITH HEPSERA. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY IN PATIENTS WHO DISCONTINUE ANTI-HEPATITIS B THERAPY, IF APPROPRIATE, RESUMPTION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

2. IN PATIENTS AT RISK OF OR HAVING UNDERLYING RENAL DYSFUNCTION, CHRONIC ADMINISTRATION OF HEPSERA MAY RESULT IN NEPHROTOXICITY. THESE PATIENTS SHOULD BE MONITORED CLOSELY FOR RENAL FUNCTION AND MAY REQUIRE DOSE ADJUSTMENT (SEE WARNINGS AND DOSAGE AND ADMINISTRATION).

Table 1. Pharmacokinetic Parameters (Mean ± SD) of Adefovir in Patients with Varying Degrees of Renal Function

Renal Function Group	Unimpaired	Mild	Moderate	Severe
Baseline Creatinine Clearance (mL/min)	> 80 (n = 7)	50 – 80 (n = 8)	30 – 49 (n = 7)	10 – 29 (n = 10)
C_{max} (ng/mL)	17.8 ± 3.22	22.4 ± 4.04	28.5 ± 8.57	51.6 ± 10.3
AUC $_{0-\infty}$ (ng*h/mL)	201 ± 40.8	266 ± 55.7	455 ± 176	1240 ± 629
CL/F (mL/min)	469 ± 99.0	356 ± 85.6	237 ± 118	91.7 ± 51.3
Cl_{renal} (mL/min)	231 ± 48.9	148 ± 39.3	63.9 ± 27.5	37.0 ± 18.4

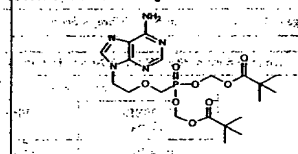
3. HIV RESISTANCE MAY EMERGE IN CHRONIC HEPATITIS B PATIENTS WITH UNRECOGNIZED OR UNTREATED HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION TREATED WITH ANTI-HEPATITIS B THERAPIES, SUCH AS THERAPY WITH HEPSERA, THAT MAY HAVE ACTIVITY AGAINST HIV (SEE WARNINGS).

4. LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

HEPSERA is the tradename for adefovir dipivoxil, a diester prodrug of adefovir. Adefovir is an acyclic nucleotide analog with activity against human hepatitis B virus (HBV).

The chemical name of adefovir dipivoxil is 9-[2-[bis[(pivaloyloxy)methoxy]phosphinyl]methoxy]ethyl]adenine. It has a molecular formula of $C_{20}H_{32}N_5O_8P$, a molecular weight of 501.48 and the following structural formula:



Adefovir dipivoxil is a white to off-white crystalline powder with an aqueous solubility of 19 mg/mL at pH 2.0 and 0.4 mg/mL at pH 7.2. It has an octanol/aqueous phosphate buffer (pH 7) partition coefficient (log p) of 1.91.

HEPSERA tablets are for oral administration. Each tablet contains 10 mg of adefovir dipivoxil and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, pregelatinized starch, and talc.

Microbiology

Mechanism of Action:

Adefovir is an acyclic nucleotide analog of adenosine monophosphate. Adefovir is phosphorylated to the active metabolite, adefovir diphosphate, by cellular kinases. Adefovir diphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate deoxyadenosine triphosphate and by causing DNA chain termination after its incorporation into viral DNA. The inhibition constant (K_i) for adefovir diphosphate for HBV DAN polymerase was 0.1 µM. Adefovir diphosphate is a weak inhibitor of human DNA polymerases α and γ with K_i values of 1.18 µM and 0.97 µM, respectively.

Antiviral Activity:

The *in vitro* antiviral activity of adefovir was determined in HBV transfected human hepatoma cell lines. The concentration of adefovir that inhibited 50% of viral DNA synthesis (IC_{50}) varied from 0.2 to 2.5 µM.

Drug Resistance:

Clinical Studies 437 & 438

Genotypic and phenotypic analyses of serum HBV DNA from adefovir dipivoxil (10 mg or 30 mg) treated HBeAg-positive patients (n = 215; study 437) and HBeAg-negative patients (n = 56; study 438) at baseline and week 48 did not identify mutations in the HBV DNA polymerase gene that may confer reduced susceptibility to adefovir. An unconfirmed increase of ≥ 1 log_{10} copies/mL in serum HBV DNA was observed in some patients. The molecular basis and/or the clinical significance for the observed unconfirmed increases are not known.

Cross-resistance:

Recombinant HBV variants containing lamivudine-resistance-associated mutations (L528M, M552I, M552V, L528M + M552V) in the HBV DNA polymerase gene were susceptible to adefovir *in vitro*. Adefovir has also demonstrated anti-HBV activity (median reduction in serum HBV DNA of 4.3 log_{10} copies/mL) against clinical isolates of HBV containing lamivudine-resistance-associated mutations (study 435). HBV variants with DNA polymerase mutations T476N and R or W501Q associated with resistance to hepatitis B immunoglobulin were susceptible to adefovir *in vitro*.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of adefovir have been evaluated in healthy volunteers and patients with chronic hepatitis B. Adefovir pharmacokinetics are similar between these populations.

Absorption:

Adefovir dipivoxil is a diester prodrug of the active moiety adefovir. Based on a cross study comparison, the approximate oral bioavailability of adefovir from a 10 mg single dose of HEPSERA is 59%.

Following oral administration of a 10 mg single dose of HEPSERA to chronic hepatitis B patients (n = 14), the peak adefovir plasma concentration (C_{max}) was 18.4 ± 6.26 ng/mL (mean ± SD) and occurred between 0.58 and 4.00 hours (median = 1.75 hours) post dose. The adefovir area under the plasma concentration-time curve ($AUC_{0-\infty}$) was 220 ± 70.0 ng•h/mL. Plasma adefovir concentrations declined in a biexponential manner with a terminal elimination half-life of 7.48 ± 1.65 hours.

The pharmacokinetics of adefovir in subjects with adequate renal function were not affected by once daily dosing of 10 mg HEPSERA over seven days. The impact of long-term once daily administration of 10 mg HEPSERA on adefovir pharmacokinetics has not been evaluated.

Effects of Food on Oral Absorption:

Adefovir exposure was unaffected when a 10 mg single dose of HEPSERA was administered with food (an approximately 1000 kcal high-fat meal). HEPSERA may be taken without regard to food.

Distribution:

In vitro binding of adefovir to human plasma or human serum proteins is ≤ 4% over the adefovir concentration range of 0.1 to 25 µg/mL. The volume of distribution at steady-state following intravenous administration of 1.0 or 3.0 mg/kg/day is 392 ± 75 and 352 ± 9 mL/kg, respectively.

Metabolism and Elimination:

Following oral administration, adefovir dipivoxil is rapidly converted to adefovir. Forty-five percent of the dose is recovered as adefovir in the urine over 24 hours at steady-state following 10 mg oral doses of HEPSERA. Adefovir is renally excreted by a combination of glomerular filtration and active tubular secretion (See Drug Interactions).

Special Populations:

Gender

The pharmacokinetics of adefovir were similar in male and female patients.

Race

Insufficient data are available to determine the effect of race on the pharmacokinetics of adefovir.

Pediatric and Geriatric Patients

Pharmacokinetic studies have not been conducted in children or in the elderly.

Renal Impairment

In subjects with moderately or severely impaired renal function or with end-stage renal disease (ESRD) requiring hemodialysis, C_{max}, AUC, and half-life ($T_{1/2}$) were increased compared to subjects with normal renal function. It is recommended that the dosing interval of HEPSERA be modified in these patients (See DOSAGE AND ADMINISTRATION).

The pharmacokinetics of adefovir in non-chronic hepatitis B patients with varying degrees of renal impairment are described in Table 1. In this study, subjects received a 10 mg single dose of HEPSERA.

[See table 1 above]

A four-hour period of hemodialysis removed approximately 35% of the adefovir dose. The effect of peritoneal dialysis on adefovir removal has not been evaluated.

Hepatic Impairment

The pharmacokinetics of adefovir following a 10 mg single dose of HEPSERA have been studied in non-chronic hepatitis B patients with hepatic impairment. There were no substantial alterations in adefovir pharmacokinetics in patients with moderate and severe hepatic impairment compared to unimpaired patients. No change in HEPSERA dosing is required in patients with hepatic impairment.

Drug Interactions:

Adefovir dipivoxil is rapidly converted to adefovir *in vivo*. At concentrations substantially higher (> 4000 fold) than those observed *in vivo*, adefovir did not inhibit any of the common human CYP450 enzymes, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Adefovir is not a substrate for these enzymes. However, the potential for adefovir to induce CYP450 enzymes is unknown. Based on the results of these *in vitro* experiments and the renal elimination pathway of adefovir, the potential for CYP450 mediated interactions involving adefovir as an inhibitor or substrate with other medicinal products is low.

The pharmacokinetics of adefovir have been evaluated following multiple dose administration of HEPSERA (10 mg once daily) in combination with lamivudine (100 mg once daily), trimethoprim/sulfamethoxazole (160/800 mg twice

Continued on next page

- The usual dose of TRUVADA is 1 tablet once a day. TRUVADA is always used with other anti-HIV medicines. If you have kidney problems, you may need to take TRUVADA less often.
- TRUVADA may be taken with or without a meal. Food does not affect how TRUVADA works. Take TRUVADA at the same time each day.
- If you forget to take TRUVADA, take it as soon as you remember that day. **Do not** take more than 1 dose of TRUVADA in a day. **Do not** take 2 doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do. **It is important that you do not miss any doses of TRUVADA or your anti-HIV medicines.**
- When your TRUVADA supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to TRUVADA and become harder to treat.
- Do not change your dose or stop taking TRUVADA without first talking with your healthcare provider. Stay under a healthcare provider's care when taking TRUVADA.
- If you take too much TRUVADA, call your local poison control center or emergency room right away.

What should I avoid while taking TRUVADA?

- **Do not breast-feed.** See "What should I tell my healthcare provider before taking TRUVADA?"
- **Avoid doing things that can spread HIV infection** since TRUVADA does not stop you from passing the HIV infection to others.
  - **Do not share needles or other injection equipment.**
  - **Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.**
  - **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom or other barrier to reduce the chance of sexual contact with semen, vaginal secretions, or blood.
- COMBIVIR, EMTRIVA, EPIVIR, EPIVIR-HBV, EPZICOM, TRIZIVIR or VIREAD.

TRUVADA should not be used with these medicines.

What are the possible side effects of TRUVADA?

TRUVADA may cause the following serious side effects (see "What is the most important information I should know about TRUVADA?"):

- **Lactic acidosis** (buildup of an acid in the blood). Lactic acidosis can be a medical emergency and may need to be treated in the hospital. **Call your doctor right away if you get signs of lactic acidosis.** (See "What is the most important information I should know about TRUVADA?")
- **Serious liver problems (hepatotoxicity),** with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Call your healthcare provider right away if you get any signs of liver problems. (See "What is the most important information I should know about TRUVADA?")
- **"Flare-ups" of Hepatitis B Virus infection,** in which the disease suddenly returns in a worse way than before, can occur if you stop taking TRUVADA. Your healthcare provider will monitor your condition for several months after stopping TRUVADA if you have both HIV and HBV infection. TRUVADA is not for the treatment of Hepatitis B Virus infection.
- **Kidney problems** If you have had kidney problems in the past or take other medicines that can cause kidney problems, your healthcare provider should do regular blood tests to check your kidneys.
- **Changes in bone mineral density (thinning bones)** It is not known whether long-term use of TRUVADA will cause damage to your bones. If you have had bone problems in the past, your healthcare provider may need to do tests to check your bone mineral density or may prescribe medicines to help your bone mineral density.

Other side effects with TRUVADA when used with other anti-HIV medicines include:

Changes in body fat have been seen in some patients taking TRUVADA and other anti-HIV medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms and face may also happen. The cause and long term health effect of these conditions are not known at this time.

The most common side effects of EMTRIVA or VIREAD when used with other anti-HIV medicines are: dizziness, diarrhea, nausea, vomiting, headache, rash, and gas. Skin discoloration (small spots or freckles) may also happen with TRUVADA.

These are not all the side effects of TRUVADA. This list of side effects with TRUVADA is not complete at this time because TRUVADA is still being studied. If you have questions about side effects, ask your healthcare provider. Report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects.

How do I store TRUVADA?

- Keep TRUVADA **and all other medicines out of reach of children.**
- Store TRUVADA at room temperature 77 °F (25 °C).
- Keep TRUVADA in its original container and keep the container tightly closed.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure small children will not find them.

General information about TRUVADA:

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TRUVADA for a condition for which it was not prescribed. Do not give TRUVADA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about TRUVADA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about TRUVADA that is written for health professionals. For more information, you may also call 1-800-GILEAD-5 or access the TRUVADA website at www.TRUVADA.com.

Do not use TRUVADA if seal over bottle opening is broken or missing.

What are the ingredients of TRUVADA?

Active Ingredients: emtricitabine and tenofovir DF

Inactive Ingredients: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The tablets are coated with Opadry II Blue Y-30-10701 containing FD&C Blue #2 aluminum lake, hypromellose, lactose monohydrate, titanium dioxide and triacetin.

℞ Only

August 2004

EMTRIVA, TRUVADA, and VIREAD are trademarks of Gilead Sciences, Inc. REYATAZ and VIDEX are trademarks of Bristol-Myers Squibb. KALETRA is a trademark of Abbott Laboratories. COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, and TRIZIVIR are trademarks of GlaxoSmithKline.

Shown in Product Identification Guide, page 313

VIREAD®

℞

[VEER-ee-ad]

(tenofovir disoproxil fumarate) Tablets

Rx Only

WARNING

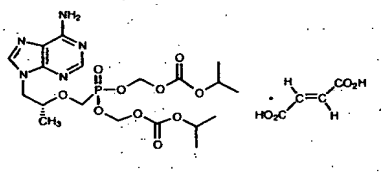
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

VIREAD® IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF VIREAD HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED VIREAD. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE VIREAD AND ARE CO-INFECTED WITH HBV AND HIV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

VIREAD is the brand name for tenofovir disoproxil fumarate (a prodrug of tenofovir) which is a fumaric acid salt of *bis*-isopropoxycarbonyloxymethyl ester derivative of tenofovir. In vivo tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25 °C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25 °C.

VIREAD tablets are for oral administration. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with a light blue colored film (Opadry II Y-30-10671-A) that is made of FD&C blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

In this insert, all dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

Microbiology

Mechanism of Action: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity In Vitro: The in vitro antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04 μM to 8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Tenofovir displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5 μM to 2.2 μM).

Drug Resistance: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in vitro. These viruses expressed a K65R mutation in reverse transcriptase and showed a 3–4 fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral agents. In treatment-naïve patients treated with Viread + lamivudine + efavirenz, viral isolates from 7/29 (24%) patients with virologic failure showed reduced susceptibility to tenofovir. In treatment-experienced patients, 14/304 (4.6%) of the VIREAD-treated patients with virologic failure showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene resulting in the K65R amino acid substitution.

Cross-resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R mutation. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption: VIREAD is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from VIREAD in fasted patients is approximately 25%. Following oral administration of a single dose of VIREAD 300 mg to HIV-1 infected patients in the fasted

Continued on next page

Table 1. Pharmacokinetic Parameters (Mean ± SD) of Tenofovir* in Patients with varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	>80 (N=3)	50–80 (N=10)	30–49 (N=8)	12–29 (N=11)
C_{max} (ng/mL)	335.4 ± 31.8	330.4 ± 61.0	372.1 ± 156.1	601.6 ± 185.3
$AUC_{0-\infty}$ (ng•hr/mL)	2184.5 ± 257.4	3063.8 ± 927.0	6008.5 ± 2504.7	15984.7 ± 7223.0
CL/F (mL/min)	1043.7 ± 15.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL_{renal} (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

*300 mg, single dose of VIREAD

Leukeran—Cont.

8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines.) *Am J Health-Syst Pharm.* 1996;53:1669-1685.

November 2003/RL-2054

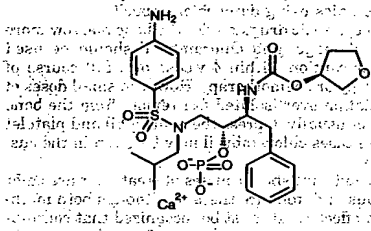
Shown in Product Identification Guide, page 316

LEXIVA®

(lex-a', va)
(fosamprenavir calcium)
Tablets

DESCRIPTION

LEXIVA (fosamprenavir calcium) is a prodrug of amprenavir, an inhibitor of human immunodeficiency virus (HIV) protease. The chemical name of fosamprenavir calcium is (3*S*)-tetrahydrofuran-3-yl (1*S*,2*R*)-3-[[(4-aminophenyl) sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy) propylcarbamate monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3*S*)(1*S*,2*R*) configuration. It has a molecular formula of $C_{25}H_{34}CaN_3O_9PS$, and a molecular weight of 623.7. It has the following structural formula:



Fosamprenavir calcium is a white to cream-colored solid with a solubility of approximately 0.31 mg/mL in water at 25°C.

LEXIVA Tablets are available for oral administration in a strength of 700 mg of fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir). Each 700-mg tablet contains the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone K30. The tablet film-coating contains the inactive ingredients hypromellose, iron oxide red, titanium dioxide, and triacetin.

MICROBIOLOGY

Mechanism of Action: Fosamprenavir is rapidly converted to amprenavir by cellular phosphatases in vivo. Amprenavir is an inhibitor of HIV-1 protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral Gag and Gag-Pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.

Antiviral Activity in Vitro: Fosamprenavir has little or no antiviral activity in vitro. The in vitro antiviral activity observed with fosamprenavir is not measurable due to trace amounts of amprenavir. The in vitro antiviral activity of amprenavir was evaluated against HIV-1 IIIB in both acutely and chronically infected lymphoblastic cell lines (MT-4, CEM-CCRF, H9) and in peripheral blood lymphocytes. The 50% inhibitory concentration (IC_{50}) of amprenavir ranged from 0.012 to 0.08 μM in acutely infected cells and was 0.41 μM in chronically infected cells (1 μM = 0.50 mcg/mL). Amprenavir exhibited synergistic anti-HIV-1 activity in combination with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir, didanosine, and zidovudine, and the protease inhibitor (PI) saquinavir, and additive anti-HIV-1 activity in combination with the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine and PIs indinavir, lopinavir, nelfinavir, and ritonavir in vitro. These drug combinations have not been adequately studied in humans. The relationship between in vitro anti-HIV-1 activity of amprenavir and the inhibition of HIV-1 replication in humans has not been defined.

Resistance: HIV-1 isolates with a decreased susceptibility to amprenavir have been selected in vitro and obtained from patients treated with fosamprenavir. Genotypic analysis of isolates from amprenavir-treated patients showed mutations in the HIV-1 protease gene resulting in amino acid substitutions primarily at positions V32I, M46I/L, I47V, I50V, I54L/M, and I84V, as well as mutations in the p7/p1 and p1/p6 Gag and Gag-Pol polyprotein precursor cleavage sites. Some of these amprenavir resistance-associated mutations have also been detected in HIV-1 isolates from antiretroviral-naive patients treated with LEXIVA. Of the 488 antiretroviral-naive patients treated with LEXIVA or LEXIVA/ritonavir, 61 patients (29 receiving LEXIVA and 32 receiving LEXIVA/ritonavir) with virological failure (plasma HIV-1 RNA ≥1,000 copies/mL on 2 occasions on or after Week 12) were genotyped. Five of the 29 antiretroviral-naive patients (17%) receiving LEXIVA without ritonavir had evidence of genotypic resistance to amprenavir: I54L/M (n = 2), I54L + L33F (n = 1), V32I + I47V (n = 1), and M46I + I47V (n = 1). No amprenavir-associated mutations were detected in antiretroviral-naive patients treated with LEXIVA/ritonavir.

Cross-Resistance: Varying degrees of cross-resistance among HIV-1 protease inhibitors have been observed. An association between virologic response at 48 weeks (HIV-1 RNA level <400 copies/mL) and PI-resistance mutations detected in baseline HIV-1 isolates from PI-experienced patients receiving LEXIVA/ritonavir twice daily (n = 88), or lopinavir/ritonavir twice daily (n = 85) in study APV30003 is shown in Table 1. The majority of subjects had previously received either one (47%) or 2 PIs (36%), most commonly nelfinavir (57%) and indinavir (53%). Out of 102 subjects with baseline phenotypes receiving twice-daily LEXIVA/ritonavir, 54% (55) had resistance to at least one PI, with 98% (54) of those having resistance to nelfinavir. Out of 97 subjects with baseline phenotypes in the lopinavir/ritonavir arm, 60% (58) had resistance to at least one PI, with 97% (56) of those having resistance to nelfinavir.

Table 1. Responders at Study Week 48 by Presence of Baseline PI Resistance-Associated Mutations*

PI-mutations†	LEXIVA/Ritonavir b.i.d. (n = 88)	Lopinavir/Ritonavir b.i.d. (n = 85)
D30N	21/22 (95%)	17/19 (89%)
N88D/S	20/22 (91%)	12/12 (100%)
L90M	16/31 (52%)	17/29 (59%)
M46I/L	11/22 (50%)	12/24 (50%)
V82A/F/T/S	2/9 (22%)	6/17 (35%)
I54V	2/11 (18%)	6/11 (55%)
I84V	1/6 (17%)	2/5 (40%)

*Results should be interpreted with caution because the subgroups were small.

†Most patients had >1 PI resistance-associated mutation at baseline.

The virologic response based upon baseline phenotype was assessed. Baseline isolates from PI-experienced patients responding to LEXIVA/ritonavir twice daily had a median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of 0.7 (range: 0.1 to 5.4, n = 62), and baseline isolates from individuals failing therapy had a median shift in susceptibility of 1.9 (range: 0.2 to 14, n = 29). Because this was a select patient population, these data do not constitute definitive clinical susceptibility break points. Additional data are needed to determine clinically relevant break points for LEXIVA.

Isolates from 15 of the 20 patients receiving twice-daily LEXIVA/ritonavir and experiencing virologic failure/ongoing replication were subjected to genotypic analysis. The following amprenavir resistance-associated mutations were found either alone or in combination: V32I, M46I/L, I47V, I50V, I54L/M, and I84V.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: Fosamprenavir is a prodrug, which is rapidly hydrolyzed to amprenavir by enzymes in the gut epithelium as it is absorbed.

The pharmacokinetic properties of amprenavir after administration of LEXIVA with or without ritonavir, have been evaluated in both healthy adult volunteers and in HIV-infected patients; no substantial differences in steady-state amprenavir concentrations were observed between the 2 populations.

Table 2. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic Parameters

Regimen	C_{max} (mcg/mL)	T_{max} (hours)*	AUC_{24} (mcg•hr/mL)	C_{min} (mcg/mL)
LEXIVA 1,400 mg b.i.d.	4.82 (4.06-5.72)	1.3 (0.8-4.0)	33.0 (27.6-39.2)	0.35 (0.27-0.46)
LEXIVA 1,400 mg q.d. plus Ritonavir 200 mg q.d.	7.24 (6.32-8.28)	2.1 (0.8-5.0)	69.4 (59.7-80.8)	1.45 (1.16-1.81)
LEXIVA 700 mg b.i.d. plus Ritonavir 100 mg b.i.d.	6.08 (5.38-6.86)	1.5 (0.75-5.0)	79.2 (69.0-90.6)	2.12 (1.77-2.54)

*Data shown are median (range).

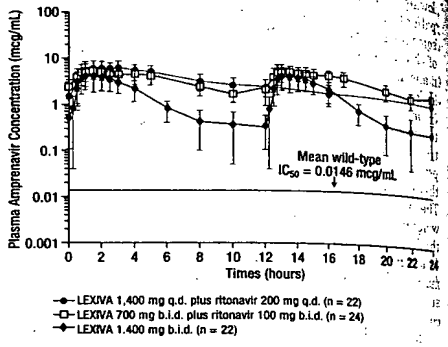
Absorption and Bioavailability: After administration of a single dose of LEXIVA to HIV-1-infected patients, the time to peak amprenavir concentration (T_{max}) occurred between 1.5 and 4 hours (median 2.5 hours). The absolute oral bioavailability of amprenavir after administration of LEXIVA in humans has not been established.

The pharmacokinetic parameters of amprenavir after administration of LEXIVA (with and without concomitant ritonavir) are shown in Table 2.

[See table 2 below]

The median plasma amprenavir concentrations of the dosing regimens over the dosing intervals are displayed in Figure 1.

Figure 1. Mean (± SD) Steady-State Plasma Amprenavir Concentrations and Mean IC_{50} Values Against HIV from Protease Inhibitor-Naive Patients (in the Absence of Human Serum)



Effects of Food on Oral Absorption: LEXIVA Tablets may be taken with or without food (see DOSAGE AND ADMINISTRATION). Administration of a single 1,400-mg dose of LEXIVA in the fed state (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate) compared to the fasted state was associated with no significant changes in amprenavir C_{max}, T_{max}, or $AUC_{0-\infty}$.

Distribution: In vitro, amprenavir is approximately 90% bound to plasma proteins, primarily to alpha$_1$-acid glycoprotein. In vitro, concentration-dependent binding was observed over the concentration range of 1 to 10 mcg/mL, with decreased binding at higher concentrations. The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism: After oral administration, fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir and inorganic phosphate prior to reaching the systemic circulation. This occurs in the gut epithelium during absorption. Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

Elimination: Excretion of unchanged amprenavir in urine and feces is minimal. Unchanged amprenavir in urine accounts for approximately 1% of the dose; unchanged amprenavir was not detectable in feces. Approximately 14% and 75% of an administered single dose of ^{14}C-amprenavir can be accounted for as metabolites in urine and feces, respectively. Two metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir is approximately 7.7 hours.

Special Populations: ***Hepatic Insufficiency:*** The pharmacokinetics of amprenavir after administration of LEXIVA have not been studied in patients with hepatic insufficiency.

The pharmacokinetics of amprenavir have been studied after administration of amprenavir given as AGENERASE® Capsules to adult patients with impaired hepatic function using a single 600-mg oral dose. The $AUC_{0-\infty}$ of amprenavir was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 mcg•hr/mL) compared with healthy volunteers (12.00 ± 4.38 mcg•hr/mL). The $AUC_{0-\infty}$ and C_{max} were significantly greater in patients with severe cirrhosis ($AUC_{0-\infty}$: 38.66 ± 16.08 mcg•hr/mL; C_{max}: 9.43 ± 2.61 mcg/mL) compared with healthy volunteers ($AUC_{0-\infty}$: 12.00 ± 4.38 mcg•hr/mL; C_{max}: 4.90 ± 1.39 mcg/mL). Based on these data, patients with impaired hepatic function receiving LEXIVA without concurrent ritonavir may require dosage reduction. There are no data on the use of LEXIVA in combination with ritonavir in patients with any degree of hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The impact of renal impairment on amprenavir elimination in adult patients has not been studied. The renal elimination of unchanged amprenavir represents approximately 1% of the administered dose; therefore, renal impairment is not expected to significantly impact the elimination of amprenavir.

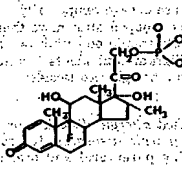
Pediatric Patients: The pharmacokinetics of amprenavir after administration of LEXIVA to pediatric patients are under investigation. There are insufficient data at this time to recommend a dose.

Geriatric Patients: The pharmacokinetics of amprenavir after administration of LEXIVA to patients over 65 years of age have not been studied.

DECADRON® Phosphate Injection R
(Dexamethasone Sodium Phosphate)

DESCRIPTION

Dexamethasone sodium phosphate, a synthetic adrenocortical steroid, is a white or slightly yellow, crystalline powder. It is freely soluble in water and is exceedingly hygroscopic. The molecular weight is 516.41. It is designated chemically as 9-fluoro-11β, 17-dihydroxy-16α-methyl-21-(phosphonooxy)pregna-1, 4-diene-3, 20-dione disodium salt. The empirical formula is $C_{22}H_{28}FNa_2O_8P$ and the structural formula is:



DECADRON* Phosphate (Dexamethasone Sodium Phosphate) injection is a sterile solution (pH 7.0 to 8.5) of dexamethasone sodium phosphate, sealed under nitrogen, and is supplied in two concentrations: 4 mg/mL and 24 mg/mL. The 24 mg/mL concentration offers the advantage of less volume in indications where high doses of corticosteroids by the intravenous route are needed.

Each milliliter of DECADRON Phosphate injection, 4 mg/mL, contains dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone. Inactive ingredients per mL: 8 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, and Water for Injection q.s., with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

Each milliliter of DECADRON Phosphate injection, 24 mg/mL, contains dexamethasone sodium phosphate equivalent to 24 mg dexamethasone phosphate or 20 mg dexamethasone. Inactive ingredients per mL: 8 mg creatinine, 10 mg sodium citrate, 0.5 mg disodium edetate, sodium hydroxide to adjust pH, and Water for Injection q.s., with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

*Registered trademark of MERCK & CO., INC.

ACTIONS

DECADRON Phosphate injection has a rapid onset but short duration of action when compared with less soluble preparations. Because of this, it is suitable for the treatment of acute disorders responsive to adrenocortical steroid therapy.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, including dexamethasone, are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

INDICATIONS

A. By intravenous or intramuscular injection when oral therapy is not feasible:

1. *Endocrine disorders*
Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).
Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used)
Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful
Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected
Congenital adrenal hyperplasia
Nonsuppurative thyroiditis
Hypercalcemia associated with cancer
2. *Rheumatic disorders*
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
Post-traumatic osteoarthritis
Synovitis of osteoarthritis
Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
Acute and subacute bursitis
Epicondylitis
Acute nonspecific tenosynovitis
Acute gouty arthritis
Psoriatic arthritis
Ankylosing spondylitis
3. *Collagen diseases*
During an exacerbation or as maintenance therapy in selected cases of:
Systemic lupus erythematosus
Acute rheumatic carditis
4. *Dermatologic diseases*
Pemphigus
Severe erythema multiforme (Stevens-Johnson syndrome)
Exfoliative dermatitis
Bullous dermatitis herpetiformis
Severe seborrheic dermatitis
Severe psoriasis
Mycosis fungoides
5. *Allergic states*
Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
Bronchial asthma
Contact dermatitis
Atopic dermatitis
Serum sickness
Seasonal or perennial allergic rhinitis
Drug hypersensitivity reactions
Urticarial transfusion reactions
Acute noninfectious laryngeal edema (epinephrine is the drug of first choice)
6. *Ophthalmic diseases*
Severe acute and chronic allergic and inflammatory processes involving the eye, such as:
Herpes zoster ophthalmicus
Iritis, iridocyclitis
Chorioretinitis
Diffuse posterior uveitis and choroiditis
Optic neuritis
Sympathetic ophthalmia
Anterior segment inflammation
Allergic conjunctivitis
Keratitis
Allergic corneal marginal ulcers
7. *Gastrointestinal diseases*
To tide the patient over a critical period of the disease in:
Ulcerative colitis (Systemic therapy)
Regional enteritis (Systemic therapy)
8. *Respiratory diseases*
Symptomatic sarcoidosis
Berylliosis
Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
Loeffler's syndrome not manageable by other means
Aspiration pneumonitis
9. *Hematologic disorders*
Acquired (autoimmune) hemolytic anemia
Idiopathic thrombocytopenic purpura in adults (I.V. only; I.M. administration is contraindicated)
Secondary thrombocytopenia in adults
Erythroblastopenia (RBC anemia)
Congenital (erythroid) hypoplastic anemia
10. *Neoplastic diseases*
For palliative management of:
Leukemias and lymphomas in adults
Acute leukemia of childhood
11. *Edematous states*
To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type, or that due to lupus erythematosus
12. *Miscellaneous*
Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
Trichinosis with neurologic or myocardial involvement
13. *Diagnostic testing of adrenocortical hyperfunction*
14. *Cerebral Edema* associated with primary or metastatic brain tumor, craniotomy, or head injury. Use in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.

B. By intra-articular or soft tissue injection:
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
Synovitis of osteoarthritis
Rheumatoid arthritis
Acute and subacute bursitis
Acute gouty arthritis
Epicondylitis
Acute nonspecific tenosynovitis
Post-traumatic osteoarthritis
C. By intralesional injection:
Keloids
Localized hypertrophic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare, and lichen simplex chronicus (neurodermatitis)
Discoid lupus erythematosus
Necrobiosis lipoidica diabeticorum
Alopecia areata
May also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

Systemic fungal infections. (See WARNINGS regarding amphotericin B.)
Hypersensitivity to any component of this product, including sulfites (see WARNINGS).

WARNINGS

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug. Anaphylactoid or hypersensitivity reactions have been reported for this DECADRON Phosphate (see ADVERSE REACTIONS). Injection DECADRON Phosphate contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions due to amphotericin B. Moreover, there have been reports in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure.

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and is to be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be instituted. If the patient is receiving steroids the dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. (See PRECAUTIONS.)

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results.

In cerebral malaria, a double-blind trial has shown that the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

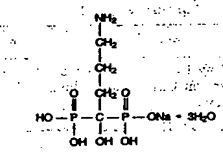
Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., in Addison's disease.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune patients on corticosteroids. In such patients who have not had these diseases, particular care should be taken to avoid exposure. The risk of developing a disseminated infection varies among individuals and can be related to the dose, route and duration of corticosteroid administration as well as to the underlying disease. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered. If exposed to measles, prophy

Fosamax—Cont.



Alendronate sodium is a white, crystalline, nonhygroscopic powder. It is soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

Tablets FOSAMAX for oral administration contain 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.

Each bottle of the oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%.

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CLINICAL PHARMACOLOGY

Mechanism of Action

Animal studies have indicated the following mode of action. At the cellular level, alendronate shows preferential localization to sites of bone resorption, specifically under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast recruitment or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radioactive [^{3}H]alendronate in bone showed about 10-fold higher uptake on osteoclast surfaces than on osteoblast surfaces. Bones examined 6 and 49 days after [^{3}H]alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women when administered after an overnight fast and 2 hours before breakfast.

FOSAMAX 70 mg oral solution and FOSAMAX 70 mg tablet are equally bioavailable.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. In studies of treatment and prevention of osteoporosis, alendronate was effective when administered at least 30 minutes before breakfast.

Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 ng/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min (64, 78; 90% confidence interval [CI]), and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric: Alendronate pharmacokinetics have not been investigated in patients <18 years of age.

Gender: Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric: Bioavailability and disposition (urinary excretion) were similar in elderly and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). **FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience with alendronate in renal failure.**

Hepatic Insufficiency: As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Drug Interactions (also see PRECAUTIONS, *Drug Interactions*)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 to 44%).

Products containing calcium and other multivalent cations are likely to interfere with absorption of alendronate.

Pharmacodynamics

Alendronate is a bisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover.

Osteoporosis in postmenopausal women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral (spinal) fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

Long-term treatment of osteoporosis with FOSAMAX 10 mg/day (for up to five years) reduced urinary excretion of markers of bone resorption, deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50% and 70%, respectively, to reach levels similar to those seen in healthy premenopausal women. Similar decreases were seen in patients in osteoporosis prevention studies who received FOSAMAX 5 mg/day. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX. In osteoporosis treatment studies FOSAMAX 10 mg/day decreased the markers of bone formation, osteocalcin and bone specific alkaline phosphatase by approximately 50%, and total serum alkaline phosphatase by approximately 25 to 30% to reach a plateau at 6 to 12 months. In osteoporosis prevention studies FOSAMAX 5 mg/day decreased osteocalcin and total alkaline phosphatase by approximately 40% and 1[illegible] spectively. Similar reductions in the rate of bone [illegible] were observed in postmenopausal women during [illegible] studies with once weekly FOSAMAX 70 mg for [illegible] ment of osteoporosis and once weekly FOSAMAX 35 for the prevention of osteoporosis. These data indicate [illegible] rate of bone turnover reached a new steady-state [illegible] the progressive increase in the total amount of [illegible] deposited within bone.

As a result of inhibition of bone resorption, asymp[illegible] reductions in serum calcium and phosphate concentr[illegible] were also observed following treatment with FOSAM[illegible] the long-term studies, reductions from baseline in [illegible] calcium (approximately 2%) and phosphate (approx[illegible] 4 to 6%) were evident the first month after the initia[illegible] FOSAMAX 10 mg. No further decreases in serum [illegible] were observed for the five-year duration of treatment; [illegible] ever, serum phosphate returned toward pretudy level[illegible] ing years three through five. Similar reductions we[illegible] served with FOSAMAX 5 mg/day. In one-year studies [illegible] once weekly FOSAMAX 35 and 70 mg, similar reduc[illegible] were observed at 6 and 12 months. The reduction in [illegible] phosphate may reflect not only the positive bone m[illegible] balance due to FOSAMAX but also a decrease in renal [illegible] phate reabsorption.

Osteoporosis in men

Treatment of men with osteoporosis with FOSA[illegible] 10 mg/day for two years reduced urinary excretion of [illegible] linked N-telopeptides of type I collagen by approx[illegible] 60% and bone-specific alkaline phosphatase by ap[illegible] mately 40%. Similar reductions were observed in a s[illegible] study in men with osteoporosis receiving once [illegible] FOSAMAX 70 mg.

Glucocorticoid-induced Osteoporosis

Sustained use of glucocorticoids is commonly ass[illegible] with development of osteoporosis and resulting fra[illegible] (especially vertebral, hip, and rib). It occurs both in [illegible] and females of all ages. Osteoporosis occurs as a re[illegible] inhibited bone formation and increased bone resorp[illegible] sulting in net bone loss. Alendronate decreases bone [illegible] tion without directly inhibiting bone formation.

In clinical studies of up to two years' duration, FOSA[illegible] and 10 mg/day reduced cross-linked N-telopeptides of [illegible] collagen (a marker of bone resorption) by approxi[illegible] 60% and reduced bone-specific alkaline phosphatase [illegible] tal serum alkaline phosphatase (markers of bone form[illegible] by approximately 15 to 30% and 8 to 18%, respectively[illegible] result of inhibition of bone resorption, FOSAMAX [illegible] 10 mg/day induced asymptomatic decreases in serum [illegible] cium (approximately 1 to 2%) and serum phosphate [illegible] proximately 1 to 8%).

Paget's disease of bone

Paget's disease of bone is a chronic, focal skeletal dis[illegible] characterized by greatly increased and disorderly bon[illegible] modeling. Excessive osteoclastic bone resorption is fol[illegible] by osteoblastic new bone formation, leading to the re[illegible] ment of the normal bone architecture by disorganized [illegible] larged, and weakened bone structure.

Clinical manifestations of Paget's disease range fro[illegible] symptoms to severe morbidity due to bone pain, bone de[illegible] mity, pathological fractures, and neurological and d[illegible] complications. Serum alkaline phosphatase, the most [illegible] quently used biochemical index of disease activity, prov[illegible] an objective measure of disease severity and respons[illegible] therapy.

FOSAMAX decreases the rate of bone resorption dir[illegible] which leads to an indirect decrease in bone formation[illegible] clinical trials, FOSAMAX 40 mg once daily for six mo[illegible] produced significant decreases in serum alkaline phos[illegible] tase as well as in urinary markers of bone collagen deg[illegible] dation. As a result of the inhibition of bone resorp[illegible] FOSAMAX induced generally mild, transient, and asy[illegible] tomatic decreases in serum calcium and phosphate.

Clinical Studies

Treatment of osteoporosis

Postmenopausal women

Effect on bone mineral density

The efficacy of FOSAMAX 10 mg once daily in postm[illegible] pausal women, 44 to 84 years of age, with osteoporosis [illegible] bar spine bone mineral density [BMD] of at least 2 stan[illegible] deviations below the premenopausal mean) was dem[illegible] strated in four double-blind, placebo-controlled clini[illegible] studies of two or three years' duration. These included [illegible] three-year, multicenter studies of virtually identical desi[illegible] one performed in the United States (U.S.) and the other [illegible] 15 different countries (Multinational), which enrolled [illegible] and 516 patients, respectively. The following graph sh[illegible] the mean increases in BMD of the lumbar spine, femo[illegible] neck, and trochanter in patients receiving FOSAM[illegible] 10 mg/day relative to placebo-treated patients at [illegible] years for each of these studies.

[See figure at top of next column]

At three years significant increases in BMD, relative to [illegible] baseline and placebo, were seen at each measurement [illegible] in each study in patients who received FOSAMAX 10 [illegible] day. Total body BMD also increased significantly in [illegible] study, suggesting that the increases in bone mass of [illegible] spine and hip did not occur at the expense of other skel[illegible] sites. Increases in BMD were evident as early as [illegible] months and continued throughout the three years of [illegible]

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...was prescribed for your particular condi... ...for another condition or give the drug to ...OSAMAX and all medicines out of the reach ...you suspect that more than the prescribed ...dose has been taken, drink a full glass of ...your local poison control center or emer... ...diately. Do not induce vomiting. Do not lie ...

...provides a summary of information about ...have any questions or concerns about ei... ...OSAMAX or osteoporosis, talk to your doctor. In ad... ...your pharmacist or other health care pro...

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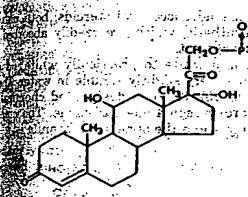
...Product Identification Guide, page 323

...CORTONE® Phosphate Injection, Sterile ... B...
...ocortisone Sodium Phosphate)

...USE AS A SINGLE DOSE VIAL ONLY

...SCRIPTION

...ocortisone sodium phosphate, a synthetic adrenocorti... ...is a white to light yellow, odorless or practically ...ess powder. It is freely soluble in water and is exceed... ...hygroscopic. The molecular weight is 486.41. It is des... ...chemically as 11β,17-dihydroxy-21-(phosphonooxy)- ...-pregnene-3,20-dione disodium salt. The empirical for... ...is $C_{21}H_{29}Na_2O_8P$ and the structural formula is:



HYDROCORTONE* Phosphate (Hydrocortisone Sodium Phosphate) injection is a sterile solution (pH 7.5 to 8.5), sealed under nitrogen, for intravenous, intramuscular, and subcutaneous administration.

Each milliliter contains hydrocortisone sodium phosphate equivalent to 50 mg hydrocortisone. Inactive ingredients per mL: 9 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, and Water for Injection, q.s. 1 mL, with 3.2 mg sodium bisulfite, 1.5 mg methylparaben, and 0.1 mg propylparaben added as preservatives.

*Registered trademark of MERCK & CO., Inc.

ACTIONS

HYDROCORTONE Phosphate injection has a rapid onset but short duration of action when compared with less soluble preparations. Because of this, it is suitable for the treatment of acute disorders responsive to adrenocortical steroid therapy.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. They are also used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS

When oral therapy is not feasible:

1. *Endocrine disorders*
   Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).
   Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used)
   Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful
   Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected
   Congenital adrenal hyperplasia
   Nonsuppurative thyroiditis
   Hypercalcemia associated with cancer
2. *Rheumatic disorders*
   As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
   Post-traumatic osteoarthritis
   Synovitis of osteoarthritis
   Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
   Acute and subacute bursitis
   Epicondylitis
   Acute nonspecific tenosynovitis
   Acute gouty arthritis
   Psoriatic arthritis
   Ankylosing spondylitis
3. *Collagen diseases*
   During an exacerbation or as maintenance therapy in selected cases of:
   Systemic lupus erythematosus
   Acute rheumatic carditis
   Systemic dermatomyositis (polymyositis)
4. *Dermatologic diseases*
   Pemphigus
   Severe erythema multiforme (Stevens-Johnson syndrome)
   Exfoliative dermatitis
   Bullous dermatitis herpetiformis
   Severe seborrheic dermatitis
   Severe psoriasis
   Mycosis fungoides
5. *Allergic states*
   Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
   Bronchial asthma
   Contact dermatitis
   Atopic dermatitis
   Serum sickness
   Seasonal or perennial allergic rhinitis
   Drug hypersensitivity reactions
   Urticarial transfusion reactions
   Acute noninfectious laryngeal edema (epinephrine is the drug of first choice)
6. *Ophthalmic diseases*
   Severe acute and chronic allergic and inflammatory processes involving the eye, such as:
   Herpes zoster ophthalmicus
   Iritis, iridocyclitis
   Chorioretinitis
   Diffuse posterior uveitis and choroiditis
   Optic neuritis
   Sympathetic ophthalmia
   Anterior segment inflammation
   Allergic conjunctivitis
   Keratitis
   Allergic corneal marginal ulcers
7. *Gastrointestinal diseases*
   To tide the patient over a critical period of the disease in:
   Ulcerative colitis (Systemic therapy)
   Regional enteritis (Systemic therapy)
8. *Respiratory diseases*
   Symptomatic sarcoidosis
   Berylliosis
   Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
   Loeffler's syndrome not manageable by other means
   Aspiration pneumonitis
9. *Hematologic disorders*
   Acquired (autoimmune) hemolytic anemia
   Idiopathic thrombocytopenic purpura in adults (I.V. only; I.M. administration is contraindicated)
   Secondary thrombocytopenia in adults
   Erythroblastopenia (RBC anemia)
   Congenital (erythroid) hypoplastic anemia
10. *Neoplastic diseases*
    For palliative management of:
    Leukemias and lymphomas in adults
    Acute leukemia of childhood
11. *Edematous states*
    To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type, or that due to lupus erythematosus
12. *Miscellaneous*
    Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
    Trichinosis with neurologic or myocardial involvement

CONTRAINDICATIONS

Systemic fungal infections (see WARNINGS regarding amphotericin B)
Hypersensitivity to any component of this product, including sulfites (see WARNINGS)

WARNINGS

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug. Anaphylactoid and hypersensitivity reactions have been reported for Injection HYDROCORTONE Phosphate (see ADVERSE REACTIONS).

Injection HYDROCORTONE Phosphate contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control life-threatening drug reactions due to amphotericin B. Moreover, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure.

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. (See PRECAUTIONS.)

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results.

In cerebral malaria, a double-blind trial has shown that the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune patients on corticosteroids. In such patients who have not had these diseases, particular care should be taken to avoid exposure. The risk of developing a disseminated infection varies among individuals and can be related to the dose, route and duration of corticosteroid administration as well as to the underlying disease. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered. If exposed to measles, prophylaxis with immune globulin (IG) may be indicated. (See the respective package inserts for VZIG and IG for complete prescribing information.)

Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfec-

Continued on next page

ripheral Neuropathy:
ntact your doctor if you experience new or worsening
mptoms of peripheral neuropathy such as numbness,
n, or a burning feeling in the feet or hands.
illennium Pharmaceuticals, Inc.
Landsdowne Street
ambridge, MA 02139
ILLENNIUM™
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ised April 2004 Rev 1
Shown in Product Identification Guide, page 324

Mission Pharmacal Company

10999 IH 10 WEST, SUITE 1000
SAN ANTONIO, TX 78230-1355

irect inquiries to:
O Box 786099
an Antonio, TX 78278–6099
OLL FREE: (800) 292-7364
10) 696-8400
AX: (210) 696-6010
or Medical Emergencies Contact:
ary Ann Walter at (210) 696-8400

ALCET® OTC

[sĭ 'sĕt]
lcium-Vit. D Dietary Supplement

W SUPPLIED
ALCET® is supplied as yellow, rectangular shaped, coated
blets in bottles of 100 (UPC 0178–0251–01).

LCET® PLUS OTC

[sĭ 'sĕt]
lcium-Iron-Zinc-Multivitamin

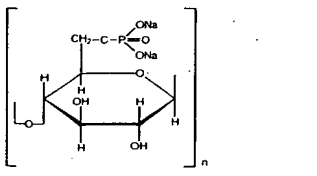
ARNING: Accidental overdose of **iron-containing** oducts is a leading cause of fatal poisoning in children der 6. Keep this product out of reach of children. In se of accidental overdose, call a doctor or poison con-rol center immediately.

W SUPPLIED
LCET PLUS is supplied as white, modified oval shaped,
ted tablets in bottles of 60 (UPC 0178-0252-60).

LCIBIND® ℞

[sĕl-bīnd]
lcium Sodium Phosphate Oral Powder

CRIPTION
lcium Sodium Phosphate (CSP), the active ingredient in
LCIBIND®, is a synthetic compound made by phosphor-
n of cellulose and has the following structural for-



n indicates the degree of polymerization and has an
value of approximately 3000. The molecular weight
onomer is 286.1 and the average molecular weight
lymer is 858,000.
inorganic bound phosphate of 31–36%, free phos-
3.5%, sodium content of approximately 11% and a
binding capacity of 1.8 mmol of Ca per gram of the
der. It has excellent ion exchange properties, the
on exchanging for calcium. When taken orally, CSP
lcium, the complex of calcium and cellulose phos-
ng excreted in feces. The dosage of CALCIBIND®
for oral administration.

PPLIED
ND®, NDC 0178-0255-30, is available for oral ad-
on in bottles of 300 grams of CSP, cream colored,
der.

CITRACAL® 250 MG + D OTC

[sĭ' trə-kăl]
Ultradense® calcium citrate-Vitamin D dietary supplement

INGREDIENTS
Calcium (as Ultradense® calcium citrate) 250 mg., polyethylene glycol, citric acid, microcrystalline cellulose, polyvinyl alcohol-part hydrolyzed, croscarmellose sodium, color added, magnesium silicate, magnesium stearate, vitamin D_3 (62.5 IU).

HOW SUPPLIED
CITRACAL® 250 MG + D is supplied as white, modified rectangle shaped, coated tablets in bottles of 150 (UPC 0178-0837-15).

CITRACAL® ◎ OTC

[sĭ'trə-kăl]
Ultradense® calcium citrate dietary supplement

INGREDIENTS
Calcium (as Ultradense® calcium citrate) 200 mg., polyethylene glycol, croscarmellose sodium, polyvinyl alcohol-part hydrolyzed, color added, magnesium silicate, magnesium stearate.

SENSITIVE PATIENTS
CITRACAL® contains no wheat, barley, yeast or rye; is sugar, dairy and gluten free.

ONE TABLET PROVIDES
200 mg. calcium (elemental), equaling 20% of the U.S. recommended daily value for adults and children 4 or more years of age.

DIRECTIONS
Take 1 to 2 tablets two times daily or as recommended by a physician, pharmacist or health professional.
Store at room temperature.

HOW SUPPLIED
CITRACAL® is supplied as white, barrel shaped, coated tablets in bottles of 100 (UPC 0178-0800-01), and bottles of 200 (UPC 0178-0800-20).
◎ = Kosher Parvae approved by Orthodox Union.

CITRACAL® Caplets + D OTC

[sĭ'trə-kăl]
Ultradense® calcium citrate - vitamin D dietary supplement

INGREDIENTS
Calcium (as Ultradense® calcium citrate) 315 mg., polyethylene glycol, croscarmellose sodium, polyvinyl alcohol-part hydrolyzed, color added, magnesium silicate, magnesium stearate, vitamin D_3 (200IU).

HOW SUPPLIED
CITRACAL® Caplets + D are supplied as white, arc rectangle shaped, coated tablets in bottles of 60 (UPC 0178-0815-60); bottles of 120 (UPC 0178-0815-12), and bottles of 180 (UPC 0178-0815-18).

CITRACAL® PLUS OTC

[sĭ' trə-kăl]
Ultradense® calcium citrate-Vitamin D-multi-mineral dietary supplement

Ingredients: Calcium (as Ultradense® calcium citrate) 250 mg., polyethylene glycol, magnesium oxide, povidone, croscarmellose sodium, polyvinyl alcohol-part hydrolyzed, hydroxypropyl methylcellulose, color added, pyridoxine hydrochloride, zinc oxide, magnesium silicate, sodium borate, manganese gluconate, copper gluconate, magnesium stearate, maltodextrin, vitamin D_3 (125 IU).

HOW SUPPLIED
CITRACAL® PLUS is supplied as white, arc rectangle shaped, coated tablets in bottles of 150 (UPC 0178-0825-15).

CITRACAL® PRENATAL Rx ℞

[sĭ'trə-kăl]
PRENATAL VITAMINS AND MINERALS

DESCRIPTION
Citracal Prenatal Rx is a scored, white, modified oval shaped multivitamin/multimineral tablet. The tablet is embossed "CITRACAL" on one side and "PN RX" on the other side.
Each tablet contains:

Vitamin A (Vitamin A palmitate)	2700 IU
Vitamin C (Ascorbic acid)	120 mg
Calcium (Calcium citrate)	125 mg
Iron (Carbonyl iron, Ferrous gluconate)	27 mg
Vitamin D_3 (Cholecalciferol)	400 IU
Vitamin E (dl-alpha tocopheryl acetate)	30 IU
Thiamin (Vitamin B_1)	3 mg
Riboflavin (Vitamin B_2)	3.4 mg
Niacinamide (Vitamin B_3)	20 mg
Pyridoxine HCl (Vitamin B_6)	20 mg
Folic Acid	1 mg
Iodine (Potassium iodide)	150 mcg
Zinc (Zinc oxide)	25 mg
Copper (Cupric oxide)	2 mg
Docusate Sodium	50 mg

INDICATIONS
CITRACAL PRENATAL Rx is a multivitamin/multimineral prescription drug indicated for use in improving the nutritional status of women prior to conception, throughout pregnancy, and in the postnatal period for both lactating and nonlactating mothers.

CONTRAINDICATIONS
This product is contraindicated in patients with a known hypersensitivity to any of the ingredients.

WARNING
Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. KEEP THIS PRODUCT OUT OF THE REACH OF CHILDREN. In case of accidental overdose, call a doctor or poison control center immediately.

Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where Vitamin B_{12} is deficient.

NOTICE
Contact with moisture may produce surface discoloration or erosion of the tablet.

PRECAUTIONS
Folic acid in doses above 0.1 mg may obscure pernicious anemia in that hematologic remission can occur while neurological manifestations progress.

ADVERSE REACTIONS
Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

DOSAGE AND ADMINISTRATION
One tablet daily or as directed by a physician.

HOW SUPPLIED
Bottles of 100 tablets (NDC 0178-0852-01)
DISPENSE IN A TIGHT, LIGHT-RESISTANT CONTAINER AS DEFINED BY THE USP/NF WITH A CHILD-RESISTANT CLOSURE.
Store at controlled room temperature.
U.S. Patent 4,814,177 Other Patent(s) pending
REV. 008010

FOSFREE® OTC

[fos 'frē]
Calcium—Iron—Multivitamin

WARNING: Accidental overdose of **iron-containing** products is a leading cause of fatal poisoning in children under 6. KEEP THIS PRODUCT OUT OF REACH OF CHILDREN. In case of accidental overdose, call a doctor or poison control center immediately. If you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

HOW SUPPLIED
FOSFREE® is supplied as yellow, modified oval shaped, coated tablets in bottles of 60 (UPC 0178-0031-60) and bottles of 120 (UPC 0178-0031-12).

IROMIN®–G OTC

[ī 'rō-min]
Hematinic plus vitamins, calcium and folic acid Dietary Supplement

WARNING: Accidental overdose of **iron-containing** products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

HOW SUPPLIED
IROMIN-G® is supplied as red, rectangular shaped coated tablets in bottles of 100 (UPC 0178-0081-01).

Continued on next page

...ure at 25°C (77°F); excursions permitted to 15–30°C ...86°F).
...USP Controlled Room Temperature. Protect from mois-...ure.

T2004-53
T2004-54

...formation for the Patient

...lnorm®
...gaserod maleate)
...ablets
...nounced ZEL-norm, te-gas-a-rod mal-ē-ate)
...e only

...ad this information carefully before you start taking ...lnorm® (ZEL-norm). Read the information you get each ...e you get more Zelnorm. There may be new information. ...This information does not take the place of talking to your ...doctor about your medical condition or treatment.

What is the most important information I should know about Zelnorm?

If you get new or worse abdominal (stomach) pain, or blood in your stools, stop taking Zelnorm right away and tell your doctor. Your doctor may need to do tests to find out if you have a serious problem with your bowel that may require special treatment or hospitalization.

Sometimes Zelnorm causes diarrhea. Stop taking Zelnorm and call your doctor right away if you get so much diarrhea that you get lightheaded, dizzy, or faint.

What is Zelnorm?

Zelnorm is a medicine for:

- The short-term treatment of women who have irritable bowel syndrome (IBS) with constipation (not enough or hard bowel movements) as their main bowel problem. Zelnorm does not work for all women who use it. Zelnorm has not been shown to work in men with IBS with constipation.
- The treatment of patients less than 65 years of age with chronic idiopathic constipation. Chronic constipation means constipation lasting over 6 months. Idiopathic constipation means constipation not due to other diseases or drugs. Zelnorm has not been shown to work in patients with chronic idiopathic constipation who are 65 years of age or older.

Zelnorm increases the movement of stools (bowel movement) through the bowels. Zelnorm does not cure IBS with constipation or chronic idiopathic constipation. For those with IBS with constipation who are helped, Zelnorm reduces pain and discomfort in the abdominal area, bloating, and constipation. For those with chronic idiopathic constipation, Zelnorm increases bowel movements, reduces straining, bloating and abdominal discomfort. If you stop taking Zelnorm, your symptoms may return within 1 or 2 weeks.

Who should not take Zelnorm?

You should not start taking Zelnorm if:

- You now have diarrhea or have diarrhea often.
- You have bad kidney or liver disease.
- You have ever had bowel obstruction (intestinal blockage), symptomatic gallbladder disease, or abdominal adhesions causing pain and/or intestinal blockage.
- You are allergic to Zelnorm or any of its ingredients. The active ingredient in Zelnorm is tegaserod maleate. The inactive ingredients are listed at the end of this leaflet.

Zelnorm may not be right for you. Tell your doctor if you:

- Are pregnant or plan to become pregnant. Zelnorm is not recommended for use by pregnant women.
- Are breast-feeding. Do not breast-feed while you are taking Zelnorm. The drug is likely to pass into breast milk.
- Are taking or planning to take any other medicines, including those you can get without a prescription.

How should I take Zelnorm?

- You should take Zelnorm twice a day on an empty stomach shortly before you eat a meal, or as your doctor prescribes it.
- For IBS with Constipation: You should take Zelnorm for 4 to 6 weeks to treat your IBS symptoms. If you feel better, your doctor may prescribe an additional 4 to 6 weeks of Zelnorm.
- For Chronic Idiopathic Constipation: You should talk to your doctor regularly about whether you need to stay on Zelnorm.
- If you miss a dose of Zelnorm, just skip that dose. Do not take two tablets to make up the missed dose. Instead, just wait until the next time you are supposed to take it and then take your normal dose.

What are the possible side effects of Zelnorm?

Headache and diarrhea were the most common side effects seen with Zelnorm.

Diarrhea was an occasional side effect of treatment with Zelnorm. Most people who got diarrhea had it during the first week after starting Zelnorm. Typically, diarrhea went away with continued therapy. If you get bad diarrhea, or if you get diarrhea together with bad cramping, abdominal pain, fainting, or dizziness, tell your doctor. Your doctor may tell you to stop taking Zelnorm or suggest other ways to manage your diarrhea.

There have been rare cases of rectal bleeding and severe abdominal pain in patients treated with Zelnorm. Some of these problems were related to insufficient blood flow to part of the bowel. It is not known if this was related to Zelnorm use.

In studies, a very small number of patients were reported to have abdominal surgery. In IBS with constipation studies there were a few more reports of abdominal surgery in patients taking Zelnorm than in patients taking a sugar pill. Most of these were related to the gallbladder. It is not known if Zelnorm may increase your chance of abdominal surgery. Gallbladder surgery has been reported to occur more often in IBS patients than in the general population. This list is not complete. Your doctor or pharmacist can give you a more complete list of possible side effects. Talk to your doctor about any side effects you may have.

General information about the safe and effective use of Zelnorm

Keep Zelnorm at room temperature. Do not use Zelnorm past the expiration date shown on the package.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Zelnorm for a condition for which it was not prescribed. Do not give Zelnorm to other people, even if they have the same symptoms that you have. This leaflet summarizes the most important information about Zelnorm. For more information, talk with your doctor. You can ask your doctor or pharmacist for information about Zelnorm that is written for health professionals. You can also contact the company that makes Zelnorm at 1-866-427-6682 or www.zelnorm.com.

Inactive Ingredients: Zelnorm is available for oral use in the following tablet formulations:

- 2-mg and 6-mg tablets (blister packs) containing the following inactive ingredients: crospovidone, glyceryl monostearate, hypromellose, lactose monohydrate, poloxamer 188, and polyethylene glycol 4000.
- 6-mg tablets (bottles) containing the following inactive ingredients: crospovidone, glyceryl behenate, hypromellose, lactose monohydrate, and colloidal silicon dioxide.

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REV: AUGUST 2004 PRINTED IN U.S.A. 89015305

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
©Novartis

Shown in Product Identification Guide, page 326

ZOMETA® Rx

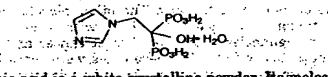
[zō-mē-ta]
(zoledronic acid) Injection
Concentrate for Intravenous Infusion
Rx only

Prescribing Information

The following prescribing information is based on official labeling in effect July 2004.

DESCRIPTION

Zometa® contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is



Zoledronic acid is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and its molar mass is 290.1g/Mol. Zoledronic acid is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

Zometa® (zoledronic acid) Injection is available in vials as a sterile liquid concentrate solution for intravenous infusion. Each 5 mL vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis.

Inactive Ingredients: mannitol, USP, as bulking agent, water for injection and sodium citrate, USP, as buffering agent.

CLINICAL PHARMACOLOGY

General

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

Pharmacokinetics

Distribution

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg Zometa® were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max}, 24 hours post infusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC_{0-24h} ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In-vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 22% and was independent of the concentration of zoledronic acid.

Metabolism

Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, <3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

In 64 patients with cancer and bone metastases on average (± s.d.) 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4-mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± SD] 403 ± 118 ng/mL vs 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng × h/mL vs 420 ± 218 ng × h/mL). The difference between the AUC means was not statistically significant.

Special Populations

Pharmacokinetic data in patients with hypercalcemia are not available.

Pediatrics: Pharmacokinetic data in pediatric patients are not available.

Geriatrics: The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases who ranged in age from 38 years to 84 years.

Race: The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer and bone metastases.

Hepatic Insufficiency: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Insufficiency: The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately impaired renal function. Compared to patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 43%. Limited pharmacokinetic data are available for Zometa in patients with severe renal impairment (creatinine clearance <30 mL/min). Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10 mL/min. Creatinine clearance is calculated by the Cockcroft-Gault formula:

$$CrCl = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \quad (\times 0.85 \text{ for female patients})$$

[See table below]

Zometa systemic clearance in individual patients can be calculated from the population clearance of Zometa, CL (L/h)=6.5(CL_{cr}/90)$^{0.4}$. These formulae can be used to predict the Zometa AUC in patients, where CL = Dose/AUC. The average AUC in patients with normal renal function was 0.42 mg*h/L (%CV 33) following a 4-mg dose of Zometa. However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed. *(See WARNINGS.)*

Pharmacodynamics

Hypercalcemia of Malignancy

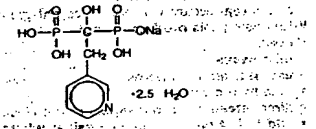
Clinical studies in patients with hypercalcemia of malignancy (HCM) showed that single-dose infusions of Zometa are associated with decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion.

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in hypercalcemia of malignancy (HCM, tumor-induced hypercalcemia) and metastatic bone disease. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in

Continued on next page

Actonel—Cont.

structure of risedronate sodium hemi-pentahydrate is the following:



·2.5 H_2O

Molecular Weight:
Anhydrous: 305.10
Hemi-pentahydrate: 350.13

Risedronate sodium is a fine, white to off-white, odorless, crystalline powder. It is soluble in water and in aqueous solutions, and essentially insoluble in common organic solvents.

Inactive Ingredients:

Crospovidone, ferric oxide red (35-mg tablets only), ferric oxide yellow (5 and 35-mg tablets only), hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action:

ACTONEL has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, ACTONEL inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (e.g., lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that ACTONEL treatment reduces bone turnover (activation frequency, i.e., the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

Pharmacokinetics:

Absorption:

Absorption after an oral dose is relatively rapid (t_{max} ~1 hour) and occurs throughout the upper gastrointestinal tract. The fraction of the dose absorbed is independent of dose over the range studied (single dose, 2.5 to 30 mg; multiple dose, 2.5 to 5 mg). Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean absolute oral bioavailability of the 30-mg tablet is 0.63% (90% CI: 0.54% to 0.75%) and is comparable to a solution. The extent of absorption of a 30-mg dose (three 10-mg tablets) when administered 0.5 hours before breakfast is reduced by 55% compared to dosing in the fasting state (no food or drink for 10 hours prior to or 4 hours after dosing). Dosing 1 hour prior to breakfast reduces the extent of absorption by 30% compared to dosing in the fasting state. Dosing either 0.5 hours prior to breakfast or 2 hours after dinner (evening meal) results in a similar extent of absorption. ACTONEL is effective when administered at least 30 minutes before breakfast.

Distribution:

The mean steady-state volume of distribution is 6.3 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [^{14}C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was in the range of 0.001% to 0.01%.

Metabolism:

There is no evidence of systemic metabolism of risedronate.

Elimination:

Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine over 28 days. Mean renal clearance is 105 mL/min (CV = 34%) and mean total clearance is 122 mL/min (CV = 19%), with the difference primarily reflecting nonrenal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. Once risedronate is absorbed, the serum concentration-time profile is multi-phasic, with an initial half-life of about 1.5 hours and a terminal exponential half-life of 480 hours. This terminal half-life is hypothesized to represent the dissociation of risedronate from the surface of bone.

Special Populations:

Pediatric:

Risedronate pharmacokinetics have not been studied in patients <18 years of age.

Gender:

Bioavailability and pharmacokinetics following oral administration are similar in men and women.

Geriatric:

Bioavailability and disposition are similar in elderly (>60 years of age) and younger subjects. No dosage adjustment is necessary.

Race:

Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency:

Risedronate is excreted unchanged primarily via the kidney. As compared to persons with normal renal function, the renal clearance of risedronate was decreased by about 70% in patients with creatinine clearance of approximately 30 mL/min. ACTONEL is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min.

Hepatic Insufficiency:

No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in rat, dog, and human liver preparations. Insignificant amounts (<0.1% of intravenous dose) of drug are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.

Pharmacodynamics:

Treatment and Prevention of Osteoporosis in Postmenopausal Women:

Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist.

The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. Osteoporosis occurs in both men and women but is more common among women following menopause. In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly-formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone formation, leading to bone loss and increased risk of bone fracture. After menopause, the risk of fractures of the spine and hip increases; approximately 40% of 50 year-old women will experience an osteoporosis-related fracture during their remaining lifetimes. After experiencing 1 osteoporosis-related fracture, the risk of future fracture increases 5-fold compared to the risk among a non-fractured population.

ACTONEL treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of ACTONEL to postmenopausal women resulted in decreases in biochemical markers of bone turnover, including urinary deoxypyridinoline/creatinine and urinary collagen cross-linked N-telopeptide (markers of bone resorption) and serum bone specific alkaline phosphatase (a marker of bone formation). At the 5-mg dose, decreases in deoxypyridinoline/creatinine were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and bone formation; decreases in bone specific alkaline phosphatase of about 20% were evident within 3 months of treatment. Bone turnover markers reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years. Bone turnover is decreased as early as 14 days and maximally within about 6 months of treatment, with achievement of a new steady-state that more nearly approximates the rate of bone turnover seen in premenopausal women. In a 1-year study comparing daily versus weekly oral dosing regimens of ACTONEL for the treatment of osteoporosis in postmenopausal women, ACTONEL 5-mg daily and ACTONEL 35-mg once a week decreased urinary collagen cross-linked N-telopeptide by 60% and 61%, respectively. In addition, serum bone-specific alkaline phosphatase was also reduced by 42% and 41% in the ACTONEL 5-mg daily and ACTONEL 35-mg once a week groups, respectively. ACTONEL is not an estrogen and does not have the benefits and risks of estrogen therapy.

As a result of the inhibition of bone resorption, asymptomatic and usually transient decreases from baseline in serum calcium (<1%) and serum phosphate (<3%) and compensatory increases in serum PTH levels (<30%) were observed within 6 months in patients in osteoporosis clinical trials. There were no significant differences in serum calcium, phosphate, or PTH levels between the ACTONEL and placebo groups at 3 years. In a 1-year study comparing daily versus weekly oral dosing regimens of ACTONEL in postmenopausal women, the mean changes from baseline at 12 months were similar between the ACTONEL 5-mg daily and ACTONEL 35-mg once a week groups, respectively, for serum calcium (0.4% and 0.7%), phosphate (-3.8% and -2.6%) and PTH (6.4% and 4.2%).

Glucocorticoid-Induced Osteoporosis:

Sustained use of glucocorticoids is commonly associated with development of osteoporosis and resulting fractures (especially vertebral, hip, and rib). It occurs in both males and females of all ages. The relative risk of a hip fracture in patients on >7.5 mg/day prednisone is more than doubled (RR = 2.27); the relative risk of vertebral fracture is increased 5-fold (RR = 5.18). Bone loss occurs most rapidly during the first 6 months of therapy with persistent but slowing bone loss for as long as glucocorticoid therapy continues. Osteoporosis occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. ACTONEL decreases bone resorption without directly inhibiting bone formation.

In two 1-year clinical trials in the treatment and prevention of glucocorticoid-induced osteoporosis, ACTONEL 5 mg decreased urinary collagen cross-linked N-telopeptide (a marker of bone resorption), and serum bone specific alkaline phosphatase (a marker of bone formation) by 50% to 55% and 25% to 30%, respectively, within 3 to 6 months after initiation of therapy.

Paget's Disease:

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disordered bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe bone pain, bone deformity, pathological fractures, and neurological disorders. Serum alkaline phosphatase, the most frequently used biochemical marker of disease activity, provides an objective measure of disease severity and response to therapy.

In pagetic patients treated with ACTONEL 30 mg/day for 2 months, bone turnover returned to normal in a majority of patients as evidenced by significant reductions in serum alkaline phosphatase (a marker of bone formation), and in urinary hydroxyproline/creatinine and deoxypyridinoline/creatinine (markers of bone resorption). Radiographic structural changes of bone lesions, especially improvement of a majority of lesions with an osteolytic front in weight-bearing bones, were also observed after ACTONEL treatment. In addition, histomorphometric data provide further support that ACTONEL can lead to a more normal bone structure in these patients.

Radiographs taken at baseline and after 6 months from patients treated with ACTONEL 30 mg daily demonstrate that ACTONEL decreases the extent of osteolysis in both the appendicular and axial skeleton. Osteolytic lesions in the lower extremities improved or were unchanged in 15/16 (94%) of assessed patients; 9/16 (56%) patients showed clear improvement in osteolytic lesions. No evidence of new fractures was observed.

CLINICAL STUDIES

Treatment of Osteoporosis in Postmenopausal Women:

The fracture efficacy of ACTONEL 5 mg daily in the treatment of postmenopausal osteoporosis was demonstrated in 2 large, randomized, placebo-controlled, double-blind studies that enrolled a total of almost 4000 postmenopausal women under similar protocols. The Multinational study (VERT MN) (ACTONEL 5 mg, n = 408) was conducted primarily in Europe and Australia; a second study was conducted in North America (VERT NA) (ACTONEL 5 mg, n = 821). Patients were selected on the basis of radiographic evidence of previous vertebral fracture, and therefore, had established disease. The average number of prevalent vertebral fractures per patient at study entry was 4 in VERT MN, and 2.5 in VERT-NA, with a broad range of baseline bone mineral density (BMD) levels. All patients in these studies received supplemental calcium 1000 mg/day. Patients with low vitamin D levels (approximately 40 nmol/L or less) also received supplemental vitamin D 500 IU/day.

Positive effects of ACTONEL treatment on BMD were also demonstrated in each of 2 large, randomized, placebo-controlled trials (BMD MN and BMD NA) in which almost 1200 postmenopausal women (ACTONEL 5 mg, n = 394) were recruited on the basis of low lumbar spine bone mass (more than 2 SD below the premenopausal mean) rather than a history of vertebral fracture.

ACTONEL 35-mg once a week (n = 485) was shown to be therapeutically equivalent to ACTONEL 5-mg daily (n = 480) in a 1-year, double-blind, multicenter study of postmenopausal women with osteoporosis. In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 4.0% (3.7, 4.3; 95% confidence interval [CI]) in the 5-mg daily group (n = 391) and 3.9% (3.6, 4.3; 95% CI) in the 35-mg once a week group (n = 387) and the mean difference between 5 mg daily and 35 mg weekly was 0.1% (-0.42, 0.55; 95% CI). The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites.

The safety and efficacy of once weekly ACTONEL 35 mg in women without osteoporosis are currently being studied, but data are not yet available.

Effect on Vertebral Fractures:

Fractures of previously undeformed vertebrae (new fractures) and worsening of pre-existing vertebral fractures were diagnosed radiographically; some of these fractures were also associated with symptoms (i.e., clinical fractures). Spinal radiographs were scheduled annually and prospectively planned analyses were based on the time to a patient's first diagnosed fracture. The primary endpoint for these studies was the incidence of new and worsening vertebral fractures across the period of 0 to 3 years. ACTONEL 5 mg daily significantly reduced the incidence of new and worsening vertebral fractures and of new vertebral fractures in both VERT NA and VERT MN at all time points (Table 1). The reduction in risk seen in the subgroup of patients who had 2 or more vertebral fractures at study entry was similar to that seen in the overall study population.

[See table 1 at top of next page]

Effect on Osteoporosis-Related Nonvertebral Fractures:

In VERT MN and VERT NA, a prospectively planned efficacy endpoint was defined consisting of all radiographically confirmed fractures of skeletal sites accepted as associated with osteoporosis. Fractures at these sites were collectively referred to as osteoporosis-related nonvertebral fractures. ACTONEL 5 mg daily significantly reduced the incidence of nonvertebral osteoporosis-related fractures over 3 years in VERT NA (8% vs. 5%; relative risk reduction 39%) and reduced the fracture incidence in VERT MN from 16% to 11%. There was a significant reduction from 11% to 7% when the

Intravenous **Dantrium** may be used postoperatively to prevent or attenuate the recurrence of signs of malignant hyperthermia when oral **Dantrium** administration is not practical. The i.v. dose of **Dantrium** in the postoperative period must be individualized, starting with 1 mg/kg or more as the clinical situation dictates.

PREPARATION

Each vial of **Dantrium Intravenous** should be reconstituted by adding 60 mL of *sterile water for injection USP (without a bacteriostatic agent), and the vial shaken until the solution is clear.* 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, and other acidic solutions are not compatible with **Dantrium Intravenous** and should not be used. The contents of the vial must be *protected from direct light and used within 6 hours* after reconstitution. Store reconstituted solutions at controlled room temperature (59°F to 86°F or 15°C to 30°C).

Reconstituted **Dantrium Intravenous** should *not* be transferred to large glass bottles for prophylactic infusion due to precipitate formation observed with the use of some glass bottles as reservoirs.

For prophylactic infusion, the required number of individual vials of **Dantrium Intravenous** should be reconstituted as outlined above. The contents of individual vials are then transferred to a larger volume sterile intravenous plastic bag. Stability data on file at Procter & Gamble Pharmaceuticals indicate commercially available sterile plastic bags are acceptable drug delivery devices. However, it is recommended that the prepared infusion be inspected carefully for cloudiness and/or precipitation prior to dispensing and administration. Such solutions should not be used. While stable for 6 hours, it is recommended that the infusion be prepared immediately prior to the anticipated dosage administration time.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

Dantrium Intravenous (NDC 0149-0734-02) is available in vials containing a sterile lyophilized mixture of 20 mg dantrolene sodium, 3000 mg mannitol, and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 mL sterile water for injection USP (without a bacteriostatic agent).

Store unreconstituted product at controlled room temperature (59°F to 86°F or 15°C to 30°C) and avoid prolonged exposure to light.

Address medical inquiries to Procter & Gamble Pharmaceuticals, Medical Communications Department, PO Box 8006, Mason, Ohio 45040-8006.

To place an order, call Procter & Gamble Pharmaceuticals Customer Service 800-448-4878.

Mfg. by: Ben Venue Laboratories
Bedford, OH 44146

Dist. By: **Procter & Gamble Pharmaceuticals,** TM Owner, Cincinnati, Ohio 45202
REVISED MAY 2001

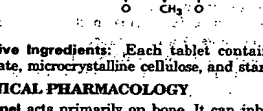
DIDRONEL®

[di'dro-nel]

(etidronate disodium)

DESCRIPTION

Didronel tablets contain either 200 mg or 400 mg of etidronate disodium, the disodium salt of (1-hydroxyethylidene) diphosphonic acid, for oral administration. This compound, also known as EHDP, regulates bone metabolism. It is a white powder, highly soluble in water, with a molecular weight of 250 and the following structural formula:



Inactive Ingredients: Each tablet contains magnesium stearate, microcrystalline cellulose, and starch.

CLINICAL PHARMACOLOGY

Didronel acts primarily on bone. It can inhibit the formation, growth, and dissolution of hydroxyapatite crystals and their amorphous precursors by chemisorption to calcium phosphate surfaces. Inhibition of crystal resorption occurs at lower doses than are required to inhibit crystal growth. Both effects increase as the dose increases.

Didronel is not metabolized. The amount of drug absorbed after an oral dose is approximately 3%. In normal subjects, plasma half-life ($t_{1/2}$ of etidronate, based on non-compartmental pharmacokinetics is 1 to 6 hours. Within 24 hours, approximately half the absorbed dose is excreted in urine; the remainder is distributed to bone compartments from which it is slowly eliminated. Animal studies have yielded bone clearance estimates up to 165 days. In humans, the residence time on bone may vary due to such factors as specific metabolic condition and bone type. Unabsorbed drug is excreted intact in the feces. Preclinical studies indicate etidronate disodium does not cross the blood-brain barrier. **Didronel** therapy does not adversely affect serum levels of parathyroid hormone or calcium.

Paget's Disease: Paget's disease of bone (osteitis deformans) is an idiopathic, progressive disease characterized by abnormal and accelerated bone metabolism in one or more bones. Signs and symptoms may include bone pain and/or deformity, neurologic disorders, elevated cardiac output and other vascular disorders, and increased serum alkaline phosphatase and/or urinary hydroxyproline levels. Bone fractures are common in patients with Paget's disease.

Didronel slows accelerated bone turnover (resorption and accretion) in pagetic lesions and, to a lesser extent, in normal bone. This has been demonstrated histologically, scintigraphically, biochemically, and through calcium kinetic and balance studies. Reduced bone turnover is often accompanied by symptomatic improvement, including reduced bone pain. Also, the incidence of pagetic fractures may be reduced, and elevated cardiac output and other vascular disorders may be improved by **Didronel** therapy.

Heterotopic Ossification: Heterotopic ossification, also referred to as myositis ossificans (circumscripta, progressiva or traumatica), ectopic calcification, periarticular ossification, or paraosteoarthropathy, is characterized by metaplastic osteogenesis. It usually presents with signs of localized inflammation or pain, elevated skin temperature, and redness. When tissues near joints are involved, functional loss may also be present.

Heterotopic ossification may occur for no known reason as in myositis ossificans progressiva or may follow a wide variety of surgical, occupational, and sports trauma (e.g., hip arthroplasty, spinal cord injury, head injury, burns, and severe thigh bruises). Heterotopic ossification has also been observed in non-traumatic conditions (e.g., infections of the central nervous system, peripheral neuropathy, tetanus, biliary cirrhosis, Peyronie's disease, as well as in association with a variety of benign and malignant neoplasms).

Clinical trials have demonstrated the efficacy of **Didronel** in heterotopic ossification following total hip replacement, or due to spinal cord injury.

— *Heterotopic ossification complicating total hip replacement* typically develops radiographically 3 to 8 weeks postoperatively in the periacapsular area of the affected hip joint. The overall incidence is about 50%; about one-third of these cases are clinically significant.

— *Heterotopic ossification due to spinal cord injury* typically develops radiographically 1 to 4 months after injury. It occurs below the level of injury, usually at major joints. The overall incidence is about 40%; about one-half of these cases are clinically significant.

Didronel chemisorbs to calcium hydroxyapatite crystals and their amorphous precursors, blocking the aggregation, growth, and mineralization of these crystals. This is thought to be the mechanism by which **Didronel** prevents or retards heterotopic ossification. There is no evidence **Didronel** affects mature heterotopic bone.

INDICATIONS AND USAGE

Didronel is indicated for the treatment of symptomatic Paget's disease of bone and in the prevention and treatment of heterotopic ossification following total hip replacement or due to spinal cord injury. **Didronel** is not approved for the treatment of osteoporosis.

Paget's Disease: **Didronel** is indicated for the treatment of symptomatic Paget's disease of bone. **Didronel** therapy usually arrests or significantly impedes the disease process as evidenced by:

— Symptomatic relief, including decreased pain and/or increased mobility (experienced by 3 out of 5 patients).

— Reductions in serum alkaline phosphatase and urinary hydroxyproline levels (30% or more in 4 out of 5 patients).

— Histomorphometry showing reduced numbers of osteoclasts and osteoblasts, and more lamellar bone formation.

— Bone scans showing reduced radionuclide uptake at pagetic lesions.

In addition, reductions in pagetically elevated cardiac output and skin temperature have been observed in some patients.

In many patients, the disease process will be suppressed for a period of at least 1 year following cessation of therapy. The upper limit of this period has not been determined.

The effects of the **Didronel** treatment in patients with asymptomatic Paget's disease have not been studied. However, **Didronel** treatment of such patients may be warranted if extensive involvement threatens irreversible neurologic damage, major joints, or major weight-bearing bones.

Heterotopic Ossification: **Didronel** is indicated in the prevention and treatment of heterotopic ossification following total hip replacement or due to spinal cord injury.

Didronel reduces the incidence of clinically important heterotopic bone by about two-thirds. Among those patients who form heterotopic bone, **Didronel** retards the progression of immature lesions and reduces the severity by at least half. Follow-up data (at least 9 months posttherapy) suggest these benefits persist.

In total hip replacement patients, **Didronel** does not promote loosening of the prosthesis or impede trochanteric reattachment.

In spinal cord injury patients, **Didronel** does not inhibit fracture healing or stabilization of the spine.

CONTRAINDICATIONS

Didronel tablets are contraindicated in patients with known hypersensitivity to etidronate disodium or in patients with clinically overt osteomalacia.

WARNINGS

Paget's Disease: In Paget's patients the response to therapy may be of slow onset and continue for months after **Didronel** therapy is discontinued. Dosage should not be increased prematurely. A 90-day drug-free interval should be provided between courses of therapy.

Heterotopic Ossification: No specific warnings.

PRECAUTIONS

General: Patients should maintain an adequate nutritional status, particularly an adequate intake of calcium and vitamin D.

Therapy has been withheld from some patients with enterocolitis since diarrhea may be experienced, particularly at higher doses.

Didronel is not metabolized and is excreted intact via the kidney. Hyperphosphatemia may occur at doses of 10 to 20 mg/kg/day, apparently as a result of drug-related increases in tubular reabsorption of phosphate. Serum phosphate levels generally return to normal 2 to 4 weeks post-therapy. There is no experience to specifically guide treatment in patients with impaired renal function. **Didronel** dosage should be reduced when reductions in glomerular filtration rates are present. Patients with renal impairment should be closely monitored. In approximately 10% of patients in clinical trials of **Didronel® I.V.** infusion (etidronate disodium) for hypercalcemia of malignancy, occasional, mild-to-moderate abnormalities in renal function (increases of > 0.5 mg/dl serum creatinine) were observed during or immediately after treatment.

Didronel suppresses bone turnover, and may retard mineralization of osteoid laid down during the bone accretion process. These effects are dose and time dependent. Osteoid, which may accumulate noticeably at doses of 10 to 20 mg/kg/day, mineralizes normally posttherapy. In patients with fractures, especially of long bones, it may be advisable to delay or interrupt treatment until callus is evident.

Paget's Disease: In Paget's patients, treatment regimens exceeding the recommended (see DOSAGE AND ADMINISTRATION) daily maximum dose of 20 mg/kg or continuous administration of medication for periods greater than 6 months may be associated with osteomalacia and an increased risk of fracture.

Long bones predominantly affected by lytic lesions, particularly in those patients unresponsive to **Didronel** therapy, may be especially prone to fracture.

Patients with predominantly lytic lesions should be monitored radiographically and biochemically to permit termination of **Didronel** in those patients unresponsive to treatment.

Drug Interactions: There have been isolated reports of patients experiencing increases in their prothrombin times when etidronate was added to warfarin therapy. The majority of these reports concerned variable elevations in prothrombin times without clinically significant sequelae. Although the relevance of these reports and any mechanism of coagulation alterations is unclear, patients on warfarin should have their prothrombin time monitored.

Carcinogenesis: Long-term studies in rats have indicated that **Didronel** is not carcinogenic.

Pregnancy: Teratogenic Effects: Pregnancy Category C. In teratology and developmental toxicity studies conducted in rats and rabbits treated with dosages of up to 100 mg/kg (5 to 20 times the clinical dose), no adverse or teratogenic effects have been observed in the offspring. Etidronate disodium has been shown to cause skeletal abnormalities in rats when given at oral dose levels of 300 mg/kg (15 to 60 times the human dose). Other effects on the offspring (including decreased live births) are at dosages that cause significant toxicity in the parent generation and are 25 to 200 times the human dose. The skeletal effects are thought to be the result of the pharmacological effects of the drug on bone. Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

There are no adequate and well-controlled studies in pregnant women. **Didronel** (etidronate disodium) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **Didronel** is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Pediatric patients have been treated with **Didronel,** at doses recommended for adults, to prevent heterotopic ossifications or soft tissue calcifications. A rachitic syndrome has been reported infrequently at doses of 10 mg/kg/day and more for prolonged periods approaching or exceeding a year. The epiphyseal

Continued on next page

IV. DOSAGE AND ADMINISTRATION

Claripel Cream should be applied to the affected areas twice daily or as directed by a physician. There is no recommended dosage for pediatric patients under 12 years of age except under the advice and supervision of a physician.

V. CONTRAINDICATIONS

Claripel Cream is contraindicated in any patient that has a prior history of hypersensitivity or allergic reaction to hydroquinone or any of the other ingredients. The safety of topical hydroquinone use during pregnancy or on children (12 years and under) has not been established.

VI. WARNINGS

A. CAUTION: Hydroquinone is a depigmenting agent which may produce unwanted cosmetic effects if not used as directed. The physician should be familiar with the contents of this insert before prescribing or dispensing this medication.

B. Test for skin sensitivity before using Claripel Cream by applying a small amount to an unbroken patch of skin and check within 24 hours. Minor redness is not a contraindication, but where there is itching, vesicle formation, or excessive inflammatory response further treatment is not advised. Close patient supervision is recommended. Contact with the eyes should be avoided. If no lightening effect is noted after two months of treatment, use of Claripel Cream should be discontinued. Claripel Cream is formulated for use as a treatment for dyschromia and should not be used for the prevention of sunburn.

C. Sunscreen use is an essential aspect of hydroquinone therapy, because even minimal sunlight sustains melanocytic activity. The sunscreens in Claripel Cream provide the necessary sun protection during therapy. During and after the use of Claripel Cream, sun exposure should be limited or sun-protective clothing should be used to cover the treated areas to prevent repigmentation.

D. Keep this and all medications out of the reach of children. In case of accidental ingestion, contact a physician or a poison control center immediately.

E. WARNING: Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

F. On rare occasions, a gradual blue-black darkening of the skin may occur. In which case, use of Claripel Cream should be discontinued and a physician contacted immediately.

VII. PRECAUTIONS

SEE WARNINGS

A. Pregnancy Category C: Animal reproduction studies have not been conducted with topical hydroquinone. It is also not known whether hydroquinone can cause fetal harm when used topically on a pregnant woman or can affect reproductive capacity. It is not known to what degree, if any, topical hydroquinone is absorbed systemically. Topical hydroquinone should be used in pregnant women only where clearly indicated.

B. Nursing mothers: It is not known whether topical hydroquinone is absorbed or excreted in human milk. Caution is advised when hydroquinone is used by a nursing mother.

C. Pediatric usage: Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

VIII. ADVERSE REACTIONS

No systemic reactions have been reported. Occasional cutaneous hypersensitivity (localized contact dermatitis) may occur, in which case the medication should be discontinued and the physician notified immediately.

IX. OVERDOSAGE

There have been no systemic reactions reported from the use of topical hydroquinone. However, treatment should be limited to relatively small areas of the body at one time, since some patients experience a transient skin reddening and a mild burning sensation which does not preclude treatment.

X. HOW SUPPLIED

Claripel Cream is available as follows:

Tube Size	NDC Number
28 gram	0145-2516-03
45 gram	0145-2516-05

REFERENCES

1. Denton, C., A.B. Lerner, and T.B. Fitzpatrick. "Inhibition of Melanin Formation by Chemical Agents." *Journal of Investigative Dermatology*. 1952; 18:119–135.

2. Jimbow, K., H. Obata, M. Pathak, and T.B. Fitzpatrick. "Mechanism of Depigmentation by Hydroquinone." *Journal of Investigative Dermatology*. 1974; 62:436–449.

3. Parrish, J.A., R.R. Anderson, F. Urbach, and D. Pitts. *UVA, Biological Effects of Ultraviolet Radiation with Emphasis on Human Responses to Longwave Ultraviolet*. Plenum Press, New York and London, 1978, p. 151.

Claripel Cream should be stored at controlled room temperature: 15°–30° C (59°–86° F).

Patent Pending

CLINDETS®

[klin-dētz']

(Clindamycin Phosphate Pledgets)

1%*

*equivalent to 1% clindamycin (10 mg/mL)

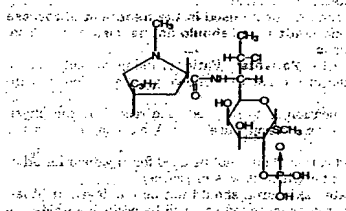
FOR EXTERNAL USE ONLY

DESCRIPTION

Clindets® (Clindamycin Phosphate Pledgets) contain clindamycin phosphate, USP at a concentration equivalent to 10 mg clindamycin per milliliter in a vehicle of isopropyl alcohol 52% v/v, propylene glycol and water. Each Clindets® pledget applicator contains approximately 1 mL of Clindamycin Phosphate Topical Solution. Clindamycin Phosphate Topical Solution has a pH range between 4.0 and 7.0.

Clindamycin phosphate is a water soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. It occurs as a white to off-white, hygroscopic, crystalline powder. It is freely soluble in water, slightly soluble in dehydrated alcohol, very slightly soluble in acetone and practically insoluble in chloroform, benzene, and ether. Clindamycin phosphate is odorless or practically odorless, and has a bitter taste.

Chemically, clindamycin phosphate is $C_{18}H_{34}ClN_2O_8PS$. It has the following structural formula:



The chemical name for clindamycin phosphate is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate). (MW=504.97)

CLINICAL PHARMACOLOGY

Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

Following multiple topical applications of clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per mL in an isopropyl alcohol and water solution, very low levels of clindamycin are present in the serum (0-3 ng/mL) and less than 0.2% of the dose is recovered in urine as clindamycin.

Clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of a Clindamycin Phosphate Pledget for 4 weeks was 597 mcg/g of comedonal material (range 0-1490). Clindamycin *in vitro* inhibits all *Propionibacterium acnes* cultures tested (MICs 0.4 mcg/mL). Free fatty acids on the skin surface have been decreased from approximately 14% to 2% following application of clindamycin.

INDICATIONS AND USAGE

Clindets are indicated in the treatment of acne vulgaris. In view of the potential for diarrhea, bloody diarrhea and pseudomembranous colitis, the physician should consider whether other agents are more appropriate. (See CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS.)

CONTRAINDICATIONS

Clindets are contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

WARNINGS

Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

Studies indicate a toxin(s) produced by *clostridia* is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.

Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition.

Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 milligrams to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind to vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin.

PRECAUTIONS

General

Clindets contain an alcohol base which will cause burning and irritation of the eyes. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucuous membranes), bathe with copious amounts of cool tap water. The solution has an unpleasant taste and caution should be exercised when applying medication around the mouth.

Clindets should be prescribed with caution in atopic individuals.

Drug Interactions

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Pregnancy: Teratogenic effects-Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin ranging from 100 to 600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to clindamycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of Clindets. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in the pediatric population under the age of 12 has not been established.

ADVERSE REACTIONS

In 18 clinical studies of various topical formulations of clindamycin phosphate using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatological events (see table below).

[See table below]

OVERDOSAGE

Topically applied Clindamycin Phosphate formulations can be absorbed in sufficient amounts to produce systemic effects. (See WARNINGS.)

DOSAGE AND ADMINISTRATION

Apply a thin film using a Clindets applicator for the application of Clindamycin Phosphate Topical Solution twice daily to affected area. More than one pledget may be used. Each pledget should be used only once and then discarded. Remove pledget from foil just before use. Do not use if the seal is broken.

Discard after single use.

Continued on next page

Treatment Emergent Adverse Event	Number of patients reporting events: Solution n=553 (%)	Gel n=148 (%)	Lotion n=160 (%)
Burning	62 (11)	15 (10)	17 (11)
Itching	36 (7)	15 (10)	17 (11)
Burning/Itching	60 (11)	# (-)	# (-)
Dryness	105 (19)	34 (23)	29 (18)
Erythema	86 (16)	10 (7)	22 (14)
Oiliness/Oily Skin	8 (1)	26 (18)	12* (10)
Peeling	61 (11)	# (-)	11 (7)

not recorded * of 126 subjects

PDR®
59
EDITION
2005

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ISBN: 1-56363-497-X

Drugs & Biologics Search Results

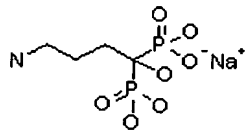
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	139212
CAS Registry No.	066376-36-1 (free acid) 121268-17-5 (triNa salt, trihydrate)
Molecular Formula	C4 H12 N O7 P2 . Na
Molecular Weight	271.0768
Highest Phase	Launched-1993
Under Active Development	

Chemical Structure



Alendronic acid sodium salt

Chemical Name/Description

(4-Amino-1-hydroxybutylidene)bisphosphonic acid sodium salt

Code Name	Generic Name	Brand Name
AHBuBP AHButBP L-670452 MK-0217 MK-217 GTH-42 (diNa salt) G-704650 (trihydrate)	Alendronate sodium Alendronic acid sodium salt	Alendros Bonalon SALES Fosamac SALES Fosamax SALES Onclast Teiroc (former Brand Name

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Treatment of Hypercalcemia Treatment of Osteoporosis Treatment of Paget's Disease		Bisphosphonates

Organization

Abiogen
Banyu
Gentili (Originator)
Merck & Co.
Merck Frosst
Merck Sharp & Dohme
Teijin

Development Status Summary DETAILS

Phase	Organization	Condition
Launched - 1993	Abiogen Merck Sharp & Dohme	Osteoporosis
Launched - 1993	Abiogen Merck Sharp & Dohme	Osteoporosis, postmenopausal
Launched - 1995	Merck & Co.	Paget's disease
Launched	Banyu	Hypercalcemia

Related Information

Drugs & Biologics 1	**Literature** 960	**Patents** 45	**Organic Synthesis** 1	**Experimental Pharmacology** 40	**Pharmacokinetics/ Metabolism** 75	**Clinical Studies** 256	

Companies **Disease**

Drugs & Biologics Search Results

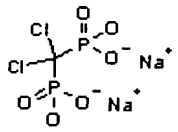
& Markets 5 Briefings 1

Records Retrieved 1 in Drugs & Biologics Options

Drugs & Biologics Search Results

Entry Number	90695
CAS Registry No.	010596-23-3 (free acid)
Molecular Formula	C H2 Cl2 O6 P2 . 2 Na
Molecular Weight	288.8548
Highest Phase	Launched-1986
Under Active Development	

Chemical Structure



Clodronate disodium

Chemical Name/Description

(Dichloromethylene)bis(phosphonic acid) disodium salt

Code Name	Generic Name	Brand Name
Cl2MDP KCO-692	Clodronate disodium	Bonefos Clasteon Clastoban Loron Lytos Ostac

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Bone Cancer Therapy Bone Diseases, Treatment of Osteoarthritis, Treatment of Treatment of Hypercalcemia Treatment of Osteoporosis		Bisphosphonates

Organization

Abiogen
Berlex (Originator)
Gentili (Originator)
Kissei
Leiras (Originator)
Procter & Gamble (Originator)
Roche
Sanofi-Aventis
Schering AG (Originator)

Product Summary

Clodronate disodium is an oral non-amino bisphosphonate originally launched in 1986 by Leiras as Bonefos® capsule: for i.v. infusion for the treatment of malignant osteolytic bone diseases. The drug was launched again in 1988 by Abi treatment of oncologic hypercalcemia and postmenopausal osteoporosis. Clodronate disodium is approved in approxi countries for the treatment of tumor-induced osteolysis and hypercalcemia. Berlex, a U.S. affiliate of Schering AG, fil application seeking approval of the drug in the U.S. for the reduction in the occurrence of bone metastases in the pos (adjuvant) treatment of breast cancer patients. In January 2005, the FDA issued an approvable letter for clodronate f indication. The company plans to request a meeting with the FDA to discuss the information that is needed to obtain submit this information as quickly as possible. Abiogen is currently evaluating clodronate sodium in phase II trials for osteoarthritis (OA). Clodronate is a potent inhibitor of osteoclast-mediated bone resorption and is able to inhibit canc osteolytic activity, thereby helping to preserve the structure of the bone. For the treatment of OA, clodronate, like ot bisphosphonates, has high affinity for hydroxyapatite which appear to play an important role in the progression of inf damage. Furthermore, additional actions on metabolic events in cells involved in the turnover of cartilage, as well as reactions, have been observed. In 1990, disodium clodronate tetrahydrate was assigned orphan drug designation by treatment of increased bone resorption due to malignancy. An additional FDA orphan drug designation was granted t

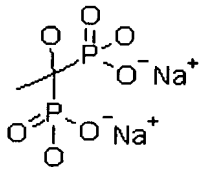
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	102157
CAS Registry No.	007414-83-7 002809-21-4 (free acid)
Molecular Formula	C2 H6 O7 P2 . 2 Na
Molecular Weight	249.9904
Highest Phase	Launched-1977
Under Active Development	

Chemical Structure



Etidronic acid disodium salt

Chemical Name/Description

(1-Hydroxyethylidene)bisphosphonic acid disodium salt

Code Name	Generic Name	Brand Name
EHDP HEBP	Etidronate disodium Etidronic acid disodium salt Xydiphone (K,Na salt)	Calcimux Didronel SALES Etidron Didrocal (cpd. with calcium

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Bone Diseases, Treatment of Treatment of Osteoporosis Treatment of Paget's Disease	Farnesyl Pyrophosphate Synthase Inhibitors	Bisphosphonates

Organization

Procter & Gamble (Originator)
Sumitomo Pharmaceuticals

Development Status Summary DETAILS

Phase	Organization	Condition
Launched - 1977	Procter & Gamble	Paget's disease
Launched - 1991	Procter & Gamble	Osteoporosis
Launched - 1998	Procter & Gamble	Osteoporosis, postmenopausal
Phase II	Sumitomo Pharmaceuticals	Bone disorders

Related Information

Targets	Literature	Patents	Experimental Pharmacology	Pharmacokinetics/ Metabolism	Clinical Studies	Companies & Markets
1	264	5	12	16	39	2

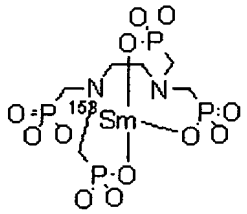
Disease Briefings 1

Records Retrieved 1 in Drugs & Biologics Options

Drugs & Biologics Search Results

Entry Number	135050
CAS Registry No.	160369-78-8 (pentaNa salt)
Molecular Formula	C6 H17 N2 O12 P4 Sm
Molecular Weight	586.0983
Highest Phase	Launched-1997
Under Active Development	

Chemical Structure



Lexidronam Sm 153

Chemical Name/Description

Pentahydrogen (OC-6-21)-[[[ethylenebis(nitrilodimethylene)]tetraphosphonato] (8-)-N,N',O(P),O(P'),O(P''),O(P''')]sa 153Sm

Code Name	Generic Name	Brand Name
CYT-424 SHR-3644 Sm-153-EDTMP	Lexidronam Sm 153 Samarium Sm 153 lexidronam	Quadramet

Therapeutic Group

Analgesic Drugs
Antiarthritic Drugs
Bone Cancer Therapy
Breast Cancer Therapy
Hematological Cancer Therapy
Multiple Myeloma Therapy
Osteosarcoma Therapy
Prostate Cancer Therapy
Rheumatoid Arthritis, Treatment of

Cellular / Molecular Mechanism

Biological / Chemical Group

Organization

CIS Bio International
Cytogen
Mayo Clinic
Memorial Sloan-Kettering Cancer Center
Nihon Schering
Northwestern University
Sanofi-Aventis (Originator)
Sidney Kimmel Cancer Center
University of Maryland

Development Status Summary DETAILS REGULATORY

Phase	Organization	Condition
Launched - 1997	Cytogen	Pain, bone
Phase III	Cytogen	Cancer, metastatic (to bone)
Phase III	Nihon Schering	Pain
Phase II	Cytogen	Hematologic/blood cancer
Phase II	Cytogen	Multiple myeloma

Phase I/II	Cytogen Northwestern University University of Maryland	Cancer, prostate
Phase I/II	Mayo Clinic	Pain, cancer
Phase I	Cytogen	Cancer, breast
Phase I	Cytogen	Osteosarcoma, localized

Related Information

Literature	Patents	Pharmacokinetics/ Metabolism	Clinical Studies	Companies & Markets	Disease Briefings
105	1	2	10	2	1

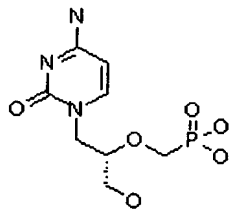
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	142187
CAS Registry No.	113852-37-2 120362-37-0 (Na salt) 149394-66-1 (dihydrate)
Molecular Formula	C8 H14 N3 O6 P
Molecular Weight	279.1876
Highest Phase	Launched-1996
Physical Properties	Fluffy white solid, m.p. 260 °C (decomp.), alpha(20,D) -97.3° (c 0.8, H2O)

Chemical Structure



Cidofovir

Under Active Development

Chemical Name/Description

(S)-1-(3-Hydroxy-2-phosphonylmethoxypropyl)cytosine
[(S)-2-(4-Amino-2-oxo-1,2-dihydropyrimidin-2-yl)-1-(hydroxymethyl)ethoxymethyl]phosphonic acid

Code Name	Generic Name	Brand Name
GS-0504 GS-504 HPMPC	Cidofovir	Forvade Vistide SALES

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Anti-Cytomegalovirus Drugs Anti-Herpes Simplex Virus Drugs Antiviral Drugs	DNA Polymerase Inhibitors	

Organization

Academy of Sciences of Czech Republic (Originator)
Gilead
National Institutes of Health
Pfizer
Rega Institute for Medical Research (Originator)

Development Status Summary DETAILS

Phase	Organization	Condition
Launched - 1996	Gilead	Retinitis, cytomegaloviral
Clinical	National Institutes of Health	Infection, smallpox

Related Information

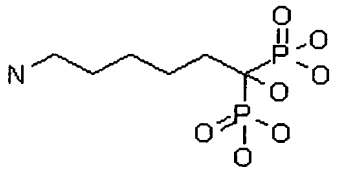
Drugs & Biologics	5	Literature	409	Patents	1	Organic Synthesis	3
Experimental Pharmacology	280	Pharmacokinetics/ Metabolism	308	Clinical Studies	13		
Companies & Markets	2	Disease Briefings	2				

Records Retrieved 1 in Drugs & Biologics **Options**

Drugs & Biologics Search Results

Entry Number	157369
CAS Registry No.	079778-41-9
Molecular Formula	C6 H17 N O7 P2
Molecular Weight	277.1483
Highest Phase	Launched-2002
Under Active Development	

Chemical Structure



Neridronic acid

Chemical Name/Description

(6-Amino-1-hydroxyhexylidene)diphosphonic acid

Code Name	**Generic Name**	**Brand Name**
AHHexBP	Neridronate Neridronic acid	Nerixia

Therapeutic Group	**Cellular / Molecular Mechanism**	**Biological / Chemical Group**
Bone Diseases, Treatment of Treatment of Osteoporosis Treatment of Paget's Disease		Bisphosphonates

Organization

Abiogen (Originator)
Abiogen (Orphan Drug)

Development Status Summary DETAILS

Phase	**Organization**	**Condition**
Launched - 2002	Abiogen	Osteogenesis imperfecta
Phase III	Abiogen	Paget's disease
Phase II	Abiogen	Osteoporosis

Related Information

Literature	**Patents**	**Organic Synthesis**	**Experimental Pharmacology**	**Clinical Studies**	**Companies & Markets**	**Disease Briefings**
25	4	1	7	8	1	1

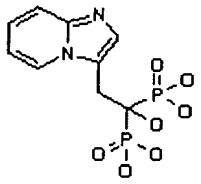
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	160070
CAS Registry No.	180064-38-4 127657-42-5 (deleted CAS) 155648-60-5 (hydrate)
Molecular Formula	C9 H12 N2 O7 P2
Molecular Weight	322.1488
Highest Phase	Phase III
Under Active Development	

Chemical Structure



Minodronic acid

Chemical Name/Description

1-Hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bis(phosphonic acid)

Code Name	Generic Name	Brand Name
Ono-5920 YH-529 YM-529	Minodronic acid	Onobis

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Bone Cancer Therapy Bone Resorption Inhibitors Multiple Myeloma Therapy Treatment of Osteoporosis		Bisphosphonates

Organization

Astellas Pharma (Originator)
Ono

Development Status Summary DETAILS

Phase	Organization	Condition
Phase III	Astellas Pharma Ono	Osteoporosis

Related Information

Drugs & Biologics 1	Literature 73	Patents 3	Organic Synthesis 1	Experimental Pharmacology 11	Pharmacokinetics/ Metabolism 1	Clinical Studies 1
Companies & Markets 2	Disease Briefings 1					

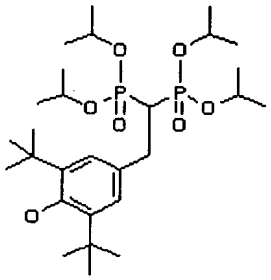
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	160285
CAS Registry No.	126411-13-0
Molecular Formula	C28 H52 O7 P2
Molecular Weight	562.6598
Highest Phase	Phase II
Under Active Development	

Chemical Structure



Apomine

Chemical Name/Description

2-(3,5-Di-tert-butyl-4-hydroxyphenyl)ethylidene-1,1-diphosphonic acid tetraisopropyl ester

Code Name	Generic Name	Brand Name
SK&F-99085 SR-45023A SR-9223i	Apomine	

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Breast Cancer Therapy Leukemia Therapy Lipoprotein Disorders, Treatment of Lung Cancer Therapy Melanoma Therapy Ovarian Cancer Therapy Prostate Cancer Therapy Treatment of Osteoporosis	Apoptosis Inducers Farnesoid X Receptor (FXR) Agonists	Bisphosphonates

Organization

Ilex Oncology (Originator)

Development Status Summary DETAILS

Phase	Organization	Condition
Phase II	Ilex Oncology	Osteoporosis

Related Information

Drugs & Biologics 1	**Targets** 1	**Literature** 44	**Patents** 5	**Organic Synthesis** 4	**Experimental Pharmacology** 2	**Pharmacokinetics/ Metabolism** 28

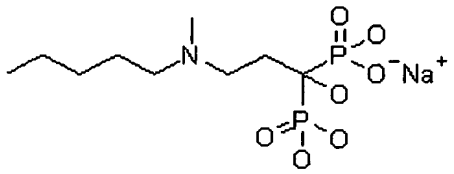
Clinical Studies 1	**Companies & Markets** 1	**Disease Briefings** 1

Records Retrieved 1 in Drugs & Biologics Options

Drugs & Biologics Search Results

Entry Number	187240
CAS Registry No.	138926-19-9 114084-78-5 (anhydrous free acid) 138844-81-2 (anhydrous)
Molecular Formula	C9 H22 N O7 P2 . Na . H2 O
Molecular Weight	359.2256
Highest Phase	Launched-1996
Under Active Development	

Chemical Structure



Ibandronic acid monosodium salt monohydra

Chemical Name/Description

[1-Hydroxy-3-(N-methyl-N-pentylamino)propylidene]bisphosphonic acid monosodium salt monohydrate

Code Name	Generic Name	Brand Name
BM-21.0955 monosodium salt monohydrate R-484 RPR-102289A Ro-200-5450	Ibandronate sodium hydrate Ibandronic acid monosodium salt monohydrate	Bondronat Boniva Destara Bonviva (former Brand Nar

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Analgesic Drugs Bone Cancer Therapy Bone Resorption Inhibitors Breast Cancer Therapy Treatment of Hypercalcemia Treatment of Osteoporosis		Bisphosphonates

Organization

Chugai (Originator)
GlaxoSmithKline
Roche (Originator)

Development Status Summary DETAILS REGULATORY I

Phase	Organization	Condition
Launched - 1996	Roche	Hypercalcemia, oncologic
Registered - 2003	Roche	Cancer, metastatic (to bone)
Registered - 2003	Roche	Osteoporosis, postmenopausal
Phase III	Roche	Pain, cancer
Phase II	Chugai	Osteoporosis

Related Information

Literature	Patents	Organic Synthesis	Experimental Pharmacology	Pharmacokinetics/ Metabolism	Clinical Studies	Companies & Markets
314	11	1	14	24	75	3

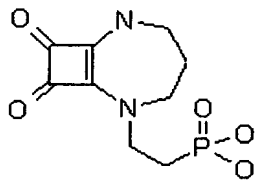
Disease Briefings 1

Records Retrieved 1 in Drugs & Biologics Options

Drugs & Biologics Search Results

Entry Number	189797
CAS Registry No.	144912-63-0
Molecular Formula	C9 H13 N2 O5 P
Molecular Weight	260.1847
Highest Phase	Phase II
Physical Properties	Hydrate, yellow solid, m.p. 260-78 °C

Chemical Structure



Perzinfotel

Under Active Development

Chemical Name/Description

2-[8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]ethylphosphonic acid

Code Name	Generic Name	Brand Name
EAA-090 WAY-126090	Perzinfotel	

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Ischemic Stroke, Treatment of Neuropathic Pain, Treatment of	NMDA Antagonists	

Organization

Wyeth Pharmaceuticals (Originator)

Development Status Summary DETAILS

Phase	Organization	Condition
Phase II	Wyeth Pharmaceuticals	Pain, neuropathic

Related Information

Drugs & Biologics 1	**Targets** 1	**Literature** 17	**Patents** 5	**Organic Synthesis** 2	**Experimental Pharmacology** 26	**Pharmacokinetics/ Metabolism** 18

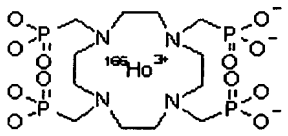
Clinical Studies 1	**Companies & Markets** 1	**Disease Briefings** 1

Records Retrieved 1 in Drugs & Biologics Options

Drugs & Biologics Search Results

Entry Number	204239
CAS Registry No.	633308-23-3
Molecular Formula	C12 H29 N4 O12 P4 . Ho
Molecular Weight	711.2731
Highest Phase	Discontinued

Chemical Structure



166Ho-DOTMP

Chemical Name/Description

1,1',1'',1'''-(1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayl)tetrakis(methylphosphonate)holmium-166Ho
Pentahydrogen [[[(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl-kappaN1,kappaN4,kappaN7,kappaN10)tetrakis(r
tetrakis(phosphonato-kappaO)](8-)]holmate(5-)-166Ho

Code Name	Generic Name	Brand Name
166Ho-DOTMP Holmium-166-DOTMP		STR

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Bone Cancer Therapy Breast Cancer Therapy Multiple Myeloma Therapy Radiation Therapy		

Organization

International Isotopes
NeoRx
NeoRx (Orphan Drug)
Sanofi-Aventis (Originator)

Development Status Summary DETAILS

No development Reported

Related Information

Literature	Patents	Organic Synthesis	Clinical Studies
37	4	1	4

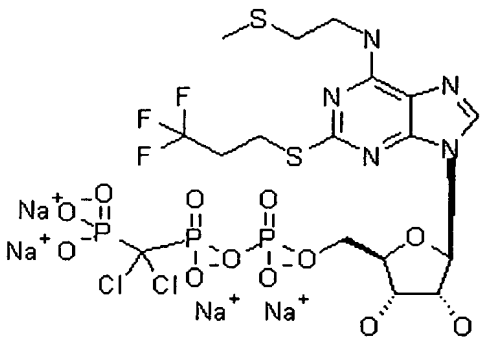
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	259645
CAS Registry No.	163706-06-7 (free acid)
Molecular Formula	C17 H21 Cl2 F3 N5 O12 P3 S2 . 4 Na
Molecular Weight	864.2899
Highest Phase	Phase II
Under Active Development	

Chemical Structure



Cangrelor sodium

Chemical Name/Description

5'-O-[[[Dichloro(phosphono)methyl](hydroxy)phosphoryloxy](hydroxy)phosphoryl]-N-[2-(methylsulfanyl)ethyl]-2-(3 trifluoropropylsulfanyl)adenosine tetrasodium salt

Code Name	Generic Name	Brand Name
AR-C69931MX	Cangrelor sodium	
Therapeutic Group	**Cellular / Molecular Mechanism**	**Biological / Chemical Group**
Antiplatelet Therapy	P2Y12 (P2T) Antagonists	

Organization

AstraZeneca Charnwood (Originator)
The Medicines Co.

Development Status Summary DETAILS

Phase	Organization	Condition
Phase II	The Medicines Co.	Percutaneous transluminal coronary angioplasty (PTC
Phase II	The Medicines Co.	Surgery, cardiac

Related Information

Targets	Literature	Patents	Organic Synthesis	Experimental Pharmacology	Pharmacokinetics/ Metabolism	Clinical Studies
1	61	2	2	4	2	3

Companies & Markets 1

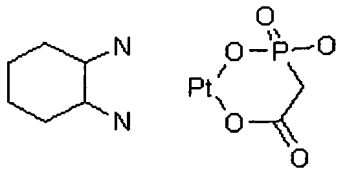
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	274705
Molecular Formula	C6 H14 N2 . C2 H3 O5 P Pt
Molecular Weight	447.2853
Highest Phase	Phase I
Under Active Development	

Chemical Structure



PADP

Chemical Name/Description

(Cyclohexane-1,2-diamine)[2-phosphonoacetato(2-)]platinum(II)

Code Name	**Generic Name**	**Brand Name**
PADP		
Therapeutic Group	**Cellular / Molecular Mechanism**	**Biological / Chemical Group**
Oncolytic Drugs	DNA-Damaging Drugs	Platinum Complexes

Organization

St. Paul Medical Center (Originator)

Related Information

Drugs & Biologics 1	**Literature 3**	**Experimental Pharmacology 9**

Search Results 2
Biomedical Literature Search Results

PADP
Drug Data Rep 1999, 21(5): 448

PADP (274705)
ACTION - Antineoplastic agent, a platinum complex with activity in vitro against several murine and human tumor cell lines (L1210, MCF-7, BT-20, DU-145, COLO-205, A-549 and SK-MEL-2), with IC50 values of 50-55 mcM. Compound produced 99.99% inhibition of clonogenic growth of L1210 cells. When given at a dose of 20 mg/kg to DBA/2 mice bearing leukemia L1210, compound increased life span by 200%. Currently undergoing phase I clinical trials.

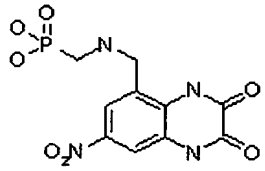
Khan, A.; et al.
Pre-clinical studies of a new compound phosphonoacetato-1,2-diaminocyclohexane platinum (II)
Proc Am Assoc Cancer Res 1999, 40: Abst 1950

Records Retrieved 1 in Drugs & Biologics **Options**

Drugs & Biologics Search Results

Entry Number	286885
CAS Registry No.	188696-80-2
Molecular Formula	C10 H11 N4 O7 P
Molecular Weight	330.1919
Highest Phase	Phase II
Under Active Development	

Chemical Structure



Becampanel

Chemical Name/Description

(7-Nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-ylmethylaminomethyl)phosphonic acid

Code Name	Generic Name	Brand Name
AMP-397 AMP-397A	Becampanel	

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Antiepileptic Drugs	AMPA Antagonists	

Organization

Novartis (Originator)

Development Status Summary DETAILS

Phase	Organization	Condition
Phase II	Novartis	Epilepsy

Related Information

Targets	Literature	Patents	Organic Synthesis	Experimental Pharmacology	Companies & Markets	Disease Briefings
1	7	2	1	5	1	1

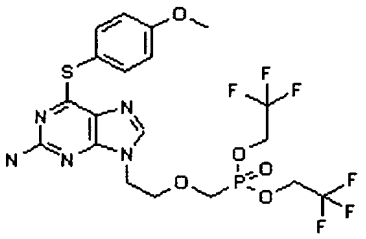
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	298405
CAS Registry No.	193681-12-8 193681-35-5 (monoHCl)
Molecular Formula	C19 H20 F6 N5 O5 P S
Molecular Weight	575.425
Highest Phase	Phase I/II

Chemical Structure



Alamifovir

Chemical Name/Description

2-[2-Amino-6-(4-methoxyphenylsulfanyl)-9H-purin-9-yl]ethoxymethylphosphonic acid bis(2,2,2-trifluoroethyl) dieste

Code Name	Generic Name	Brand Name
LY-582563 MCC-478	Alamifovir	

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Anti-Hepatitis B Virus Drugs	DNA Polymerase Inhibitors	

Organization

Lilly
Mitsubishi Pharma (Originator)

Development Status Summary DETAILS

No development Reported

Related Information

Drugs & Biologics	Literature	Patents	Organic Synthesis	Experimental Pharmacology	Clinical Studies
1	20	4	1	16	1

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Drugs & Bi

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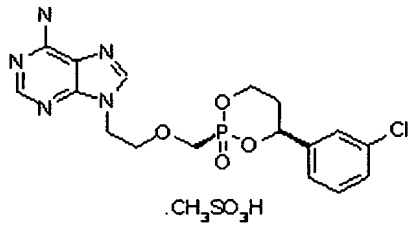
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	309134
CAS Registry No.	625095-61-6 371778-91-5 (racemic free base) 625095-60-5 (free base) 625095-69-4 (succinate) 625095-70-7 (tartrate) 625095-71-8 (tartrate) 625095-72-9 (monomaleate)
Molecular Formula	C17 H19 Cl N5 O4 P . C H4 O3 S
Molecular Weight	519.9007
Highest Phase	Phase II
Under Active Development	

Chemical Structure



Pradefovir mesylate

Chemical Name/Description

9-[2-[(2R,4S)-4-(3-Chlorophenyl)-2-oxido-1,3,2-dioxaphosphinan-2-ylmethoxy]ethyl]adenine mesylate

Code Name	Generic Name	Brand Name
ICN-2001-3	Hepavir B	
MB-06866	Pradefovir mesylate	
MB-6866	Remofovir mesylate	

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Anti-Hepatitis B Virus Drugs Chemical Delivery Systems		

Organization

Metabasis (Originator)
Valeant

Development Status Summary DETAILS

Phase	Organization	Condition
Phase II	Metabasis Valeant	Hepatitis B

Related Information

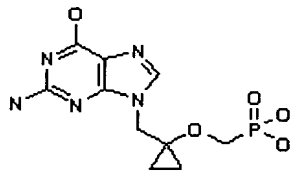
Drugs & Biologics 1	**Literature** 21	**Patents** 4	**Organic Synthesis** 2	**Pharmacokinetics/ Metabolism** 149	**Clinical Studies** 2	**Companies & Markets** 2	**Disease Briefings** 1

Records Retrieved 1 in Drugs & Biologics Options

Drugs & Biologics Search Results

Entry Number	325502
CAS Registry No.	441785-24-6
Molecular Formula	C10 H14 N5 O5 P
Molecular Weight	315.2246
Highest Phase	Phase II
Under Active Development	

Chemical Structure



LB-80317

Chemical Name/Description

1-(2-Amino-6-hydroxy-9H-purin-9-ylmethyl)cyclopropyloxymethylphosphonic acid
1-(Guanin-9-ylmethyl)cyclopropyloxymethylphosphonic acid

Code Name	Generic Name	Brand Name
ANA-317 LB-80317		

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Anti-Hepatitis B Virus Drugs		

Organization

LG Chem (Originator)

Development Status Summary DETAILS

Phase	Organization	Condition
Phase II	LG Chem	Hepatitis B

Related Information

Drugs & Biologics 3	Literature 6	Patents 1	Organic Synthesis 1	Experimental Pharmacology 10	Pharmacokinetics/ Metabolism 36	Companies & Markets 1

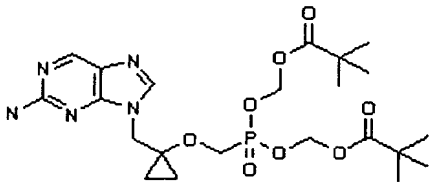
Disease Briefings 1

Records Retrieved 1 in Drugs & Biologics Options

Drugs & Biologics Search Results

Entry Number	325503
CAS Registry No.	441785-26-8
Molecular Formula	C22 H34 N5 O8 P
Molecular Weight	527.5116
Highest Phase	Phase II
Under Active Development	

Chemical Structure



LB-80380

Chemical Name/Description

Bis(2,2-dimethylpropionic acid) 1-(2-amino-9H-purin-9-ylmethyl)cyclopropoxymethylphosphorylbis(oxymethylene) di 1-(2-Amino-9H-purin-9-ylmethyl)cyclopropoxymethylphosphonic acid bis(pivaloyloxymethyl) diester

Code Name	Generic Name	Brand Name
ANA-380 LB-80380 PMCDG dipivoxil		

Therapeutic Group	Cellular / Molecular Mechanism	Biological / Chemical Group
Anti-Hepatitis B Virus Drugs		

Organization

Anadys
LG Chem (Originator)

Development Status Summary DETAILS

Phase	Organization	Condition
Phase II	Anadys LG Chem	Hepatitis B

Related Information

Drugs & Biologics 4	**Literature** 12	**Patents** 1	**Organic Synthesis** 1	**Experimental Pharmacology** 7	**Pharmacokinetics/ Metabolism** 36	**Clinical Studies** 3
Companies & Markets 2	**Disease Briefings** 1					

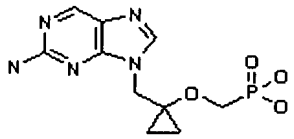
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	325505
CAS Registry No.	441785-25-7
Molecular Formula	C10 H14 N5 O4 P
Molecular Weight	299.2256
Highest Phase	Phase II

Chemical Structure



LB-80331

Chemical Name/Description

1-(2-Amino-9H-purin-9-ylmethyl)cyclopropyloxymethylphosphonic acid

Code Name

LB-80331
PMCDG

Generic Name

Brand Name

Therapeutic Group

Anti-Hepatitis B Virus Drugs

Cellular / Molecular Mechanism

Biological / Chemical Group

Organization

LG Chem (Originator)

Development Status Summary DETAILS

No development Reported

Related Information

Drugs & Biologics	Literature	Patents	Organic Synthesis	Experimental Pharmacology	Pharmacokinetics/ Metabolism
3	5	1	1	3	36

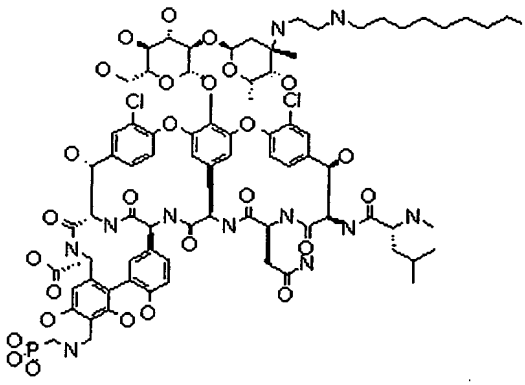
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	339576
CAS Registry No.	560130-42-9 372151-71-8 (free base) 380636-75-9 (hydrochloride)
Molecular Formula	C80 H106 Cl2 N11 O27 P . Cl H
Molecular Weight	1792.108
Highest Phase	Phase III
Under Active Development	

Chemical Structure



Telavancin hydrochloride

Chemical Name/Description

N3''-[2-(Decylamino)ethyl]-29-(phosphonomethylaminomethyl)vancomycin monohydrochloride (3S,6R,7R,22R,23S,26S,36R,38aR)-3-(2-Amino-2-oxoethyl)-10,19-dichloro-44-[2-O-[3-[2-(decylamino)ethylamino]-2,3,6-trideoxy-alpha-L-lyxo-hexopyranosyl]-beta-D-glucopyranosyloxy]-7,22,28,30,32-pentahydroxy-6-[(2R)-4-meth (methylamino)pentanoylamino]-2,5,24,38,39-pentaoxo-29-[(phosphonomethyl)aminomethyl]-2,3,4,5,6,7,23,24,25,2 tetradecahydro-8,11:18,21-dietheno-23,36-(iminomethano)-22H-13,16:31,35-dimetheno-1H,13H-[1,6,9]oxadiazacy [4,5-m][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid monohydrochloride

Code Name	Generic Name	Brand Name
TD-6424 THRX-597472	Telavancin hydrochloride	Arbelic
Therapeutic Group	**Cellular / Molecular Mechanism**	**Biological / Chemical Group**
Antibiotics		Glycopeptides

Organization

Theravance (Originator)

Development Status Summary DETAILS

Phase	Organization	Condition
Phase III	Theravance	Infection, Staphylococcus aureus (methicillin-resistar
Phase III	Theravance	Infection, skin

Related Information

Literature	46	Patents	5	Organic Synthesis	3	Experimental Pharmacology	252
Pharmacokinetics/ Metabolism	192	Clinical Studies	5	Companies & Markets	1		

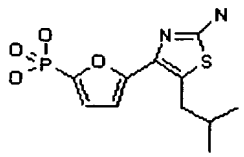
Records Retrieved 1 in Drugs & Biologics

Options

Drugs & Biologics Search Results

Entry Number	339652
CAS Registry No.	261365-11-1 261365-09-7 (monoHBr salt) 389057-53-8 (hydrobromide)
Molecular Formula	C11 H15 N2 O4 P S
Molecular Weight	302.2895
Highest Phase	Phase II
Under Active Development	

Chemical Structure



MB-05032

Chemical Name/Description

5-(2-Amino-5-isobutylthiazol-4-yl)-2-furylphosphonic acid

Code Name	**Generic Name**	**Brand Name**
MB-05032		

Therapeutic Group	**Cellular / Molecular Mechanism**	**Biological / Chemical Group**
Type 2 Diabetes, Agents for	Fructose-1,6-Bisphosphatase Inhibitors	

Organization

Metabasis (Originator)
Sankyo

Development Status Summary DETAILS

Phase	**Organization**	**Condition**
Phase II	Metabasis Sankyo	Diabetes type 2

Related Information

Drugs & Biologics	**Targets**	**Literature**	**Patents**	**Companies & Markets**
1	1	4	2	2